

UNIVERSITY of
TASMANIA

MENZIES 
Institute for Medical Research

**ASSESSMENT OF HIP STRUCTURE AND MUSCULATURE
USING MRI AND DXA IMAGES FROM TASOAC COHORT**

BY

HARBEER AHEDI

BAMS, PG diploma biomedical sciences

(Masters Part 1)



A thesis submitted in fulfilment of the degree of
Doctor of Philosophy (Medical research)

Menzies Institute for Medical Research

University of Tasmania

Hobart, Tasmania, Australia



The research work presented in this thesis was supervised by

Primary supervisor

Prof Graeme Jones, M.D,

Professional Research Fellow

Head, Musculoskeletal Unit

Menzies Institute for Medical Research, University of Tasmania

Medical Science 2 Building, Liverpool Street, Hobart, 7000, Australia

Co-supervisor

A/Prof Leigh Blizzard, PhD

Senior Statistician

Menzies Institute for Medical Research, University of Tasmania

Medical Science 2 Building, Liverpool Street, Hobart, 7000, Australia

Co-supervisor

Dr. Dawn Aitken, PhD

Post-Doctoral research fellow

NHMRC Early Career Researcher

Menzies Institute for Medical Research, University of Tasmania

Medical Science 2 Building, Liverpool Street, Hobart, 7000, Australia

Statements and declaration



Statement of originality

This thesis contains no material, which has been accepted for a degree or diploma by the university or any other institution, except by the way of background information and duly acknowledged in the thesis. To the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis nor does the thesis contain any material that infringes copyright.

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All research associated with this thesis abides by the International and Australian codes on human and animal experimentation, and full ethical approval from the relevant institutions was obtained for all studies outlined in this thesis. All individual participants provided written informed consent for involvement in the respective research studies.

Harbeer Ahedi

19 July 2016

Statement of Authorship

The following papers are incorporated into chapters of this thesis and were either published or submitted for publication in peer reviewed scientific journals during the course of PhD candidature.

Paper presented in chapter 4

Ahedi H, Aitken D, Blizzard L, Cicuttini F, Jones G (2013); A population-based study of the association between hip bone marrow lesions, high cartilage signal, and hip and knee pain. *Journal Clinical Rheumatology* 33:369-376

Author contributions

Harbeer Ahedi	Conception and design, data collection, data analyses and interpretation, and manuscript preparation and revisions.
Dawn Aitken	Study conception and design, data interpretation, critical revision of manuscript.
Leigh Blizzard	Statistical expertise, data analyses and critically revised the manuscript.
Flavia Cicuttini	Interpretation of data and critical revision
Graeme Jones	Study conception and design, data interpretation, critical revision of manuscript.

Paper presented in chapter 5

Ahedi H, Aitken D, Blizzard L, Cicuttini F, Jones G (2013); The association between hip bone marrow lesions and bone mineral density: a cross-sectional and longitudinal population-based study. *Osteoarthritis Cartilage* 19:838-838

Author contributions

Harbeer Ahedi	Conception and design, data collection, data analyses and interpretation, and manuscript preparation and revisions.
Dawn Aitken	Study conception and design, data interpretation, critical revision of manuscript.

Leigh Blizzard	Statistical expertise, data analyses and critically revised the manuscript.
Flavia Cicuttini	Interpretation of data and critical revision
Graeme Jones	Study conception and design, data interpretation, critical revision of manuscript.

Paper presented in chapter 6

Ahedi H, Aitken D, Blizzard, L, Ding C, Cicuttini F and Jones G; Correlates of hip cartilage defects: A cross-sectional study in older adults.

Published in Journal of Rheumatology (*in press*)

Author contributions

Harbeer Ahedi	Conception and design, data collection, data analyses and interpretation, and manuscript preparation and revisions.
Dawn Aitken	Study conception and design, data interpretation, critical revision of manuscript.
Leigh Blizzard	Statistical expertise, data analyses and critically revised the manuscript.
Chang-hai Ding	Study conception and design, critical revision of the manuscript.
Flavia Cicuttini	Interpretation of data and critical revision
Graeme Jones	Study conception and design, data interpretation, critical revision of manuscript.

Paper presented in chapter 7

Ahedi H, Aitken D, Blizzard L, Cicuttini F, Jones G; Chapter 7 Hip effusion-synovitis and its cross-sectional and longitudinal associations with hip pain, cartilage damage, subchondral BMLs and early radiographic hip OA.

Submitted to APLAR journal of Rheumatology, June 2016

Author contributions

Harbeer Ahedi	Conception and design, data collection, data analyses and interpretation, and manuscript preparation and revisions.
Dawn Aitken	Study conception and design, data interpretation, critical revision of manuscript.
Leigh Blizzard	Statistical expertise, data analyses and critically revised the manuscript.
Flavia Cicuttini	Interpretation of data and critical revision
Graeme Jones	Study conception and design, data interpretation, critical revision of manuscript.

Paper presented in chapter 8

Ahedi H, Aitken D, Scott D, Blizzard L, Cicuttini F, Jones G (2014); The association between hip muscle cross-sectional area, muscle strength, and bone mineral density.

Published in: Calcified Tissue International; 95: 64-72.

Author contributions

Harbeer Ahedi	Conception and design, data collection, data analyses and interpretation, and manuscript preparation and revisions.
Dawn Aitken	Study conception and design, data interpretation, critical revision of manuscript.
David Scott	Interpretation of data and critical revision.
Leigh Blizzard	Statistical expertise, data analyses and critically revised the manuscript.
Flavia Cicuttini	Interpretation of data and critical revision.
Graeme Jones	Study conception and design, data interpretation, critical revision of manuscript.

Paper presented in chapter 9

Ahedi H, Aspden R, Blizzard L, Aitken D, Blizzard L, Saunders F, Cicuttini F, Jones G, Gregory J; “Hip shape as a predictor of osteoarthritis progression in a prospective population cohort,”

Submitted to Arthritis Care and Research, June 2016

Author contributions

Harbeer Ahedi	Conception and design, data collection, data analyses and interpretation, and manuscript preparation and revisions.
Richard Aspden	Study conception and design, data interpretation, critical revision of manuscript.
Leigh Blizzard	Statistical expertise, data analyses and critically revised the manuscript.
Fiona Saunders	Study conceptions and design second observer in reliability study, critical revision of manuscript.
Dawn Aitken	Interpretation of data and critical revision of manuscript.
Flavia Cicuttini	Interpretation of data and critical revision.
Graeme Jones	Study conception and design, data interpretation, critical revision of manuscript.
Jenny Gregory	Study conception and design, data interpretation, critical revision of manuscript.

I, the undersigned agree with the above stated contributions for each of the above published (or submitted) peer-reviewed manuscripts contained within this thesis.

Prof Graeme Jones

Primary supervisor

Menzies Institute for Medical Research

Scientific Presentations arising from this thesis

International

- 2012 The European League of Against Rheumatism (EULAR)
“A Population Based Study Of The Association Between Hip Bone Marrow Lesions And Pain.”
 Berlin Germany
 (Poster presentation)
- 2012 American College of Rheumatology (ACR)
“Hip Bone Marrow Lesions (BMLS) and Bone Mineral Density: A cross-sectional and Longitudinal Population Based Study”
 Washington D.C
 (Poster presentation)
- 2013 Australian and New Zealand Bone and Mineral Society (ANZBMS)
“Cross-sectional Correlations Between Hip Muscles, Muscle Strength And Bone Mineral Density.”
 Melbourne, Australia
 (Oral presentation)
- 2013 Australian and New Zealand Bone and Mineral Society (ANZBMS)
“Hip Bone Marrow Lesions (BMLS) and Bone Mineral Density: A cross-sectional and Longitudinal Population Based Study”
 Melbourne, Australia
 (Poster presentation)
- 2014 Osteoarthritis Research Society International (OARSI) World Congress
“The Association Between Hip Cartilage Defects, Clinical, MRI-detected Structural Abnormities And Radiological findings”
 Paris, France
 (Poster Presentation)
- 2014 Osteoarthritis Research Society International (OARSI) World Congress
“The Association Between Hip Effusion and Clinical, MRI and Radiological Findings”

Paris, France

(Poster Presentation)

- 2015 Osteoarthritis Research Society International (OARSI) world congress
“Hip Shape Associates with Hip Pain And Early Structural And Radiological Changes At The Hip In An Australian Community Based Sample”
 Seattle, United States
 (Poster presentation)

National

- 2012 Australian Rheumatology Association (ARA)
“Hip Bone Marrow Lesions (BMLS) and Bone Mineral Density: A cross-sectional and Longitudinal Population Based Study”
 Canberra, Australia
 (Poster presentation)
- 2013 Sharing Excellence in Research (SEiR), University of Tasmania
“Hip Bone Marrow Lesions (BMLS) and Bone Mineral Density: A cross-sectional and Longitudinal Population Based Study”
 Hobart, Tasmania, Australia
 Poster Presentation

Awards resulting from this thesis

Year	Award
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2011	Australian Government Postgraduate Award (APA)
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2014	Osteoarthritis Research Society International (OARSI) Collaborative scholarship
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2015	Research Conference support scheme (UTAS)
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List of abbreviations

AAM	Active Appearance modeling
ALP	Alkaline phosphatase
ACR	American College of Rheumatology
ASM	Active Shape Modeling
BMD	Bone Mineral Density
BME	Bone Marrow Edema
BML	Bone Marrow Lesions
BMI	Body Mass Index
CI	Confidence Interval
CRP	C-reactive Protein
CSA	Cross-sectional Area
CT	Computed Tomography
CV	Coefficient of variation
DXA	Dual Energy X-ray Absorptiometry
ECM	Extracellular Matrix
ESR	Erythrocyte Sedimentation Rate
FAI	Femoroacetabular impingement
GF	Growth factors
HA	Hyaluronic Acid
HOOS	Hip disability and Osteoarthritis Outcome Score
ICC	Intra class Correlation Coefficient
ICTP	C-terminal cross-linking telopeptide
K-L	Kellgren-Lawrence
Micro CT	Micro Computer Tomography
MJS	Minimal Joint Space
MRI	Magnetic Resonance Imaging

NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OC	Osteocalcin
OP	Osteoporosis
OR	Odds Ratio
OST	Osteophytes
PG	Proteoglycan
PINP	Procollagen Type 1 N-terminal propeptide
PR	Prevalence Ratio
pQCT	Peripheral Quantitative Computed Tomography
RCTs	Randomized Clinical Trials
RDOA	Rapidly Destructive Hip OA
ROA	Radiographic Osteoarthritis
ROI	Region of interest
ROM	Range of Motion
SF	Synovial Fluid
SM	Synovial Membrane
SSM	Statistical Shape Modeling
STIR	Short tau Inversion Recovery
TASOAC	Tasmanian Older Adult Cohort
THR	Total Hip Replacement
TKR	Total Knee Replacement
US	Ultra sound
WOMAC	Western Ontario and McMaster Universities Index of Osteoarthritis
YLDs	Years lived with disability
ZA	Zoledronic Acid

Abstract

Introduction

Osteoarthritis (OA) is a multifactorial musculoskeletal disorder and its aetiology is under investigation. Current research and therapeutic interventions for hip OA are limited. In early or advanced stages of hip OA, imaging techniques can be used to scrutinize overall structural and muscular changes in the joint such as bone marrow lesions (BMLs), hip cartilage defects, hip effusion-synovitis, bone shape and muscle health. Investigating these factors can provide information on interactive pathways vital for understanding the aetiology of OA. This thesis reports the results of six such investigations.

Materials and Methods

The Tasmanian Older Adult Cohort (TASOAC) is a large population based cohort study initiated in 2002. Older adults aged 50-80 years (51% female, mean age 62yrs) were enrolled into the study at baseline (Phase 1) with a first follow-up approximately 3 years later (Phase 2), a second follow up (Phase 3) approximately 5 years from baseline and a third follow up (Phase 4) approximately 10 years from baseline. Hip and knee pain was assessed using the WOMAC (Western Ontario and McMaster Universities Osteoarthritis). Pedometers and a dynamometer were used to measure physical activity and muscle strength respectively. Hip structural abnormalities and hip muscle cross-sectional area (CSA) were assessed from MRI scans. Bone mineral density (BMD) was estimated by dual-energy x-ray absorptiometry (DXA). Morphological shape of the hip was assessed by Active Shape Modelling (ASM) imaging software and radiographic hip OA (ROA) was determined from X-rays.

Results

The first two studies focus on hip BMLs and their cross-sectional and longitudinal associations with hip and knee pain, high cartilage signal and BMD. Overall, the proportion of hip BMLs at the femoral and/or acetabular site was 28%. About 8% of the population had a large hip BML. In the first study, those with large hip BMLs had greater hip pain. Incidence of larger hip BMLs (femoral and acetabular) was associated with an increase in hip pain. On the other hand, resolution of femoral BMLs was associated with a decrease in knee pain.

Additionally, 1 S.D increase in hip BML size was associated with worsening hip pain. High cartilage signal intensity was strongly associated with hip BMLs but not with hip pain. This study identified that hip BMLs associate not only with hip and knee pain but also with early changes in the hip cartilage. In the second study, irrespective of size, hip BMLs were found to be associated with local (total hip and femoral neck) BMD but not with distant (spine) BMD. Femoral BMLs were associated with higher femoral neck BMD while acetabular BMLs were associated with lower hip and femoral neck BMD. This novel study suggests that hip BMLs located in two different compartments might represent bone areas undergoing different pathological changes.

In the third study, correlates of hip cartilage defects were examined. About 76% of the subjects had a hip cartilage defect. Any and grade 2 hip cartilage defects were associated with higher prevalence of hip pain. Any hip cartilage defects associated with lower muscle strength, particularly among men. The associations of grade 1 defect with high cartilage signal were stronger for men than for women. However, associations between grade 1 defects and BMLs were equivalent in both sexes. Grade 2 defects were linked with several outcomes such as hip BML, larger hip effusion-synovitis and hip ROA (in men), and lower steps per day. This study indicates that cartilage defects/damage, especially grade 2 hip cartilage defects are associated with major clinical and structural risk factors relevant to hip OA even in the general population.

The fourth study describes the cross-sectional and longitudinal correlates of hip effusion-synovitis. Cross-sectionally, presence of hip effusion-synovitis at multiple sites was associated with presence of hip pain, and hip cartilage defects were associated with greater hip effusion-synovitis CSA. No other associations were found. Longitudinally, independently of each other, persistent hip BMLs and incident hip cartilage defects predicted larger hip effusion-synovitis size. However, change in hip pain from baseline to follow up and baseline hip ROA were not associated with hip effusion-synovitis. Additionally, baseline hip cartilage defects were associated with worsening hip BMLs at follow up. Similarly, baseline hip BMLs were associated with hip cartilage defects at follow-up. Overall, these results suggest that hip cartilage defects, hip BMLs and hip effusion-synovitis share possible causal pathways and the extent of hip effusion-synovitis might influence hip pain.

The fifth study explored the link between hip musculature (hip muscle CSA), muscle strength and bone mass (BMD). Among older adults, hip flexor CSA had the strongest association with BMD of the hip. The associations for pectineus and sartorius hip muscles CSA with BMD were stronger for women in comparison to men. Most of hip muscles CSA were associated with muscle strength and muscle strength was weakly associated with BMD. These findings suggest that for older adults, muscle bulk contributes to hip bone mass more so than muscle strength and maintaining muscle mass would aid in preservation of bone health.

The sixth and the final study focused on hip morphology (shape) and its associations with various outcomes. Using Active shape modelling (ASM) imaging software and SHAPE software, hip shape was assessed and the first six principal components (modes) describing the variations in measurements of hip shape were extracted. These modes explained 68% of total hip shape variations in the sample population. At baseline, modes 1, 2, 4 and 6 were associated with hip ROA, modes 1, 3, 4 and 6 correlated with hip cartilage volume and all except mode 2 with muscle strength. Higher mode 1, and lower mode 3 and 6 scores at baseline predicted greater hip pain at follow-up and higher mode 1 and mode 2 scores were associated with hip effusion-synovitis. Greater scores for modes 2 (decreasing acetabular coverage) and 4 (non-spherical femoral head) at baseline predicted 10-year total hip replacement (THR); while mode 4 alone correlated with bone marrow lesions (BMLs), effusion-synovitis, and increased cartilage signal.

Conclusions

Overall, structural changes are slow and relatively uncommon in the preclinical stages of hip OA. Nevertheless, hip BMLs, hip cartilage defects, high cartilage signal and hip effusion-synovitis are inter-related and contribute to changes in the subchondral bone; with a probable role in the pathogenesis of hip OA. Additionally, muscle bulk and strength could aid in preservation of bone density and assessing bone shape using ASM could benefit in improving assessment and monitoring of disease progression and identifying those at higher risk of OA.

Dedication

I dedicate this thesis to my father (Late) Mr. Gursave Singh Ahedi.

Acknowledgements

I would like to express my sincere gratitude to my Primary Supervisor Prof Graeme Jones. I am grateful for his insightful comments and encouragement, but also for the hard question which incited me to widen my research from various perspectives.

A/Prof Leigh Blizzard, there is nothing I can say would justify his supervision, his role as my teacher, his friendship and his support. Thus, I would only say, “*He is statistically significant!*”

I am very grateful Dr Dawn Aitken. She is an ideal ‘*model*’ to inspire other PhD students and I really appreciate her guidance, perseverance and initiative.

Without the precious support of all my three supervisors it would not be possible to conduct this research.

Many thanks to Dr Laura Laslett, for all her support and guidance during my PhD.

I would like to extend my appreciation to Prof Flavia Cicuttini, Prof Chang-hai Ding, and Dr David Scott for their valuable input into my research.

I would like to express my deep gratitude, to all the participants of the TASOAC cohort and all the funding bodies for providing me financial support. .. These funding bodies include National Health and Medical Research Council of Australia, Tasmanian Community Fund, Masonic Centenary Medical Research Foundation, Royal Hobart Hospital Research Foundation and Arthritis Foundation of Australia. Australian Government for granting me the APA (Australian Post Graduate Award) and the UTAS and Menzies Travel/conference funding.

A special thanks to OARSI (Osteoarthritis International Research Society) for granting me collaborative research award in 2014.

Many thanks to my primary supervisor for giving me the chance to develop some excellent national and international research collaborations. I would like to acknowledge and extend sincere my gratitude towards Prof Richard Aspden, Dr Jenny Gregory, Dr Fiona Saunders, Prof Rebecca Barr, from the University of Aberdeen. During my three months stay in Aberdeen they provided me a fantastic opportunity to join their team, gave me a great opportunity to develop not only as a researcher but also as an individual.

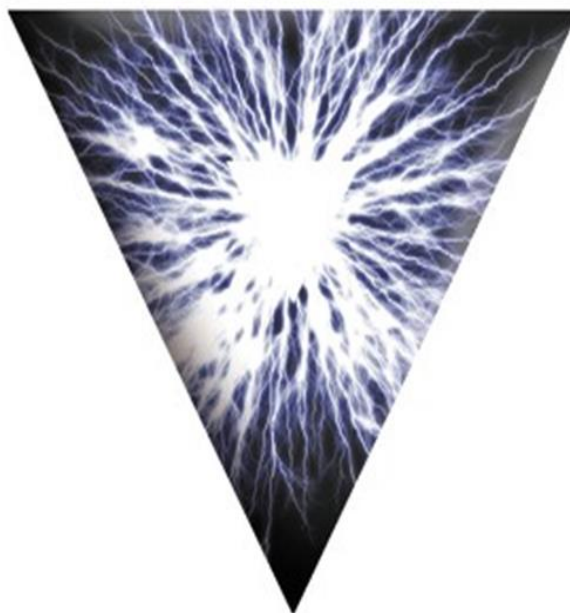
I am very grateful to Prof Tania Winzenberg who helped me develop my second international collaboration. I am very obliged towards Prof Beirma-Zentia, A/Prof Mirenke Middlekoop and Ewrin Waarsing from the University of ERASMUS for allowing me to join their research team and providing me their research facilities and expertise during my stay in The Netherlands

A sincere thanks to my loving brother (Mr. Uttam Singh Ahedi), my caring sister-in-law (Mrs Poonam Ahedi) and to all my beautiful nieces (Gurleen and Jasleen) and nephews (Ricky, Harshman and Jasveer).

My PhD, has not always been an easy journey. I have faced several tough situations but I have always had some excellent friends and they will always remain my family no matter where I go from here on. I wholeheartedly thank Dr Quan Hyauh, Dr Sonja Nikolic, Dr. Mithun Rajeshkar, William Celluar, Anitra Wilson, Kira Peterson, Dr Hazel King, Shwetha D' Souza, and Dr. Kay Ngo for their extensive friendship, love and never ending support.

Mom (Late Mrs. Tarseval Kaur Ahedi), I will always love you and I am grateful to you for everything you did!

Chapter 1 : Literature review



Definitions

Osteoarthritis (OA) is one of the most prevalent forms of chronic and painful arthritis. Traditionally, OA was labeled as a degenerative non-inflammatory disease with cartilage loss as the central pathologic feature.¹ This concept has been '*remodeled*' mainly due to the introduction of MRI-based studies which demonstrated that pathogenesis of OA involves all the joint tissues with active anabolic and catabolic processes.¹⁻³ Thus, OA is now defined as a disease of the whole organ/joint involving cartilage, subchondral bone, ligaments, menisci, peri-articular muscles, peripheral nerves and synovium. Furthermore, as OA progresses, abnormality in one component of the joint leads to changes in other components resulting in irreversible damage to the joint as a whole.⁴

Epidemiology of OA

OA is a slow and progressive musculoskeletal disease with a diverse aetiology, targeting single or multiple sites. OA commonly affects the knee, hip, spine⁴ and hand.⁵ Worldwide, about 10% of the population suffers from OA.⁶ It's the 6th most common cause of disability⁷ and one of the predominant causes of functional decline not only in aging but also in working population.^{8, 9} In Australia, 1.9 million people were reported to suffer from OA in 2012. Furthermore, it is projected that by 2034, OA would be one of the four most common and fastest growing musculoskeletal disorders.⁹

Overall impact of OA

The prevalence and incidence of OA is higher in women than in men.^{10, 11} Worldwide estimates of OA in men and women aged more than 65 years is 9.6% and 18% respectively. The incidence of OA, (irrespective of age) for men was 1.75 per 1000 population and for women 2.95 per 1000 population.¹¹ When it comes to joints affected by OA, prevalence rates of knee OA are the highest in comparison to OA at the hip, hand, and spine.¹¹

Along with an increase in prevalence, the socio-economic impact of OA is steadily rising. In Australia, arthritis is the fourth most expensive group of diseases costing around 2.6 billion dollars annually.¹² There is no adequate monitoring for the indirect costs and most of this expenditure is on hospitalisation and surgical procedures.¹² For instance, in 2007 about

40,000 knee and hip replacement procedures were performed.¹³ However, in 2012 this number doubled to 85,000 joint replacements for both knee and hip, with each procedure costing an average of \$15,000–\$31,900.¹⁴

OA is not life threatening, but the burden of the disease is substantial. An OA patient experiences not only pain and disability but may also experience an overall loss of health, psychological distress, reduced quality of life and loss of leisure time. These factors add towards loss of productivity mainly due to absenteeism and reduced work capacity.⁹ Thus, not surprisingly, years lived with disability (YLDs) in those with either knee or hip OA were greater in comparison to healthy people, and YLDs jumped from 10 million in 1990 to 17.1 million in 2010.¹⁰

Clinical Symptoms

Joint pain is the major clinical symptom in OA. It's usually episodic during early stages but with disease progression, pain becomes chronic.¹⁵ Other symptoms may include joint stiffness, joint instability, tenderness, crepitus, muscle weakness and variable degrees of inflammation.^{2, 16} Together, these symptoms cause major difficulties in daily activities such as working, walking, climbing stairs and housekeeping.

Risk factors

The pathophysiology of OA is driven by both systemic and extrinsic risk factors.¹⁷ Age is a primary, non-modifiable risk factor for OA. In general, over 30-50% of adults over the age of 65 years develop OA.¹⁸⁻²⁰ Ageing and OA are inter-related but not interdependent²¹ because rather than directly causing OA, age related changes in the joint make it susceptible towards other risk factors such as injury. Sex is another key risk factor for this musculoskeletal condition. In comparison to men, women tend to have a higher risk of incidence and severity of OA.^{7, 9-11, 22} Biological factors rather than hormonal factors may have a greater influence, as studies show that hormone replacement therapies have no impact on OA.^{7, 22}

Twin studies have demonstrated heritability estimates of OA ranging from 40-60% and ascertain that genetics have a significant role in OA.²³⁻²⁶ Surprisingly, these estimates are greater for hip and hand OA than for knee OA²⁵ and it is hypothesized there may be certain genes protective against the development of knee OA.²⁷ Thus, knee OA may be more

dependent on extrinsic risk factors rather than genetics in certain races. However, this notion needs to be confirmed as a recent study has demonstrated that the offspring of subjects who underwent total knee replacement (TKR) had a greater risk of developing knee OA.²⁴ Overall, a strong link between genetics and OA has been identified. However, OA is influenced by multiple loci (specific location of a gene) and each loci has a small effect ($OR < 1.2$). Hence, for genetic mapping of OA, a very large sample size would be needed to discover any rare large-effect mutations.²³

With genetics playing a major role, it's not surprising studies have demonstrated a variation in prevalence of OA across races and ethnicity. For example, older adults from China, in comparison with those from the US, had a lower prevalence of hip²⁸ and hand OA.²⁹ Nevertheless, the prevalence of lateral knee OA was higher in both Chinese men and women compared to Caucasians.³⁰ In the US, African Americans were more likely to develop knee OA than non-Hispanic whites³¹ and Caucasians.³²

Meta-analyses based on clinical and population-based studies show obesity is a significant risk factor for the incidence of OA.^{7, 33, 34} However, when it comes to disease progression it might be more of a mediator rather than a driving factor.^{33, 34} Obesity is strongly linked with knee and hand OA, but not with hip OA. In comparison to knee OA, the association between hand OA and obesity is weaker.³⁵ This link between OA and obesity may be due to the involvement of biomechanical factors.^{36, 37} Additionally, studies show that excess leptin generated due to adiposity causes a decrease in the synthesis of extracellular matrix (ECM) and directly affects the cartilage and indirectly causes cartilage degeneration.³⁵⁻³⁸ Not surprisingly, bone marrow of the cancellous bone of the femoral head in those with end-stage hip OA had higher fat mass.³⁹ Thus, metabolic factors such as obesity and adiposity have a deleterious impact on the bone and cartilage.

Micronutrients such as vitamin D have multiple roles in the musculoskeletal system. Studies demonstrated that those with lower levels of vitamin D and exposure to sun could be more likely to develop OA^{40, 41} and moderate vitamin D deficiency is associated with pain at both the hip and knee.^{42, 43} In addition, previous studies based on other micronutrients, such as vitamin C, demonstrated that it was protective against cartilage degeneration⁴⁴ and incidence of OA⁴⁵ and is also associated with lower knee pain.⁴⁶ However, these findings are questionable because recent clinical trials show that intake of micronutrients (such as

Vitamin A, Vitamin C, Vitamin D or Vitamin E) separately or in a combination have no effect on arthritis or OA.^{[42](#), [43](#), [47](#), [48](#)}

Injury is a very common risk factor that places young, middle and elderly populations at a higher risk of developing OA. In older adults, a high impact injury involving many tissues is a significant risk factor for the development of accelerated knee OA.^{[49](#)} Although, less prevalent than knee injury, hip injury estimates a five-fold risk of incidence and progression of hip OA.^{[50](#), [51](#)} While injury might trigger OA, changes in joint alignment (a key determinant of load distribution) is also a well-known mechanical risk factor for OA progression.^{[52](#)} In OA, cartilage loss along with a decrease in joint space causes disproportionate transmission of loads leading to joint misalignment and deformities.^{[53](#), [54](#)}

Generally speaking, it is well demonstrated that OA is of a heterogeneous nature which makes it difficult to manage or control. Additionally, with several existing risk factors, two or more of these factors could be interdependent creating a pool of individuals who are more exposed to this disabling disease.

Interrelationship between OA and osteoporosis (OP)

OA and osteoporosis (OP) are common musculoskeletal disorders that may coexist within one population^{[55](#)}. Nevertheless, their inter-relationship still remains unresolved, as a few reports suggest that there is an inverse relationship between the two while others demonstrate that all the subjects with OA may not necessarily develop OP.^{[55-59](#)} For instance, a study revealed that women who had sustained a recent fracture were less likely to develop radiographic OA^{[57](#)}. These findings were supported by another study which found that those with OP had lower odds of knee OA.^{[58](#)} Nevertheless, other studies demonstrated that although there is an association between OA and increase in BMD, OA may not be protective against fractures.^{[56](#), [59](#), [60](#)}

The link between OP and OA may depend on various pathophysiological mechanisms, including genetic mechanisms. Recent studies have suggested that OA and OP might share genetic components and a few OA susceptibility genes have been shown to be associated with the disparity in BMD.^{[61](#)} In addition, subjects with high bone mass (HBM) may be more susceptible towards higher prevalence of hip OA and osteophytosis (multiple osteophytes).^{[62](#)}

Further observations may provide clues into the pathogenesis of OA and how it relates to OP and vice versa.

Changes in BMD are possible in those with OA but specific OP may or may not be found, and as discussed above these may be linked to several factors. A few recent studies have found sclerotic bone in women with end-stage knee OA who had a bone marrow lesion (BMLs).⁶³ This small study put forth a new hypothesis, but it is unknown if BMLs are the link between OA and OP. Similarly, studies have found that in subjects with and without hip OA there is a variation in muscle strength and reduction in muscle size⁶⁴. Both, muscle strength and muscle size influence bone mass^{65, 66} and these three factors are inter-related with each other. Perhaps, this might be another cause of loss of bone mass in those with OA. Further details about BMLs, muscle size or strength and BMD have been discussed in other sections of this thesis.

Treatment and management

Overall, non-pharmacological and pharmacological treatments have been suggested for OA but pharmacological interventions such as non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics may be more effective in managing symptoms of OA.⁶⁷⁻⁷⁰ However, there is a steady rise in evidence suggesting that a balance of both non-pharmacological and pharmacological interventions could be more beneficial for patients with OA. Intra-articular (IA) corticosteroids or hyaluronic acid (HA) injections can be used to manage moderate to severe OA⁷¹ but their long-term efficiency is questionable.⁶⁸ There is an increased emphasis that bone-active treatments such as bisphosphonates could be effective in OA, but these are still in developmental stages.⁷²⁻⁷⁴ With limited effective treatments for OA, in advanced stages, due to pain and complete loss of joint function, joint replacement surgery is the only option.

Although, the major risk factors of OA have been identified, current treatments fail because these are targeted on symptoms rather than disease process. Also, there is limited knowledge regarding the mechanisms behind pathophysiology of OA.

Hip OA

Hip is the second most affected site by OA, reported in approximately one out of four older adults. Hip OA, may be divided into a continuum of four stages: an asymptomatic molecular phase, pre-radiographic phase, radiographic phase and final end-stage.^{1, 20, 75} Nevertheless, the progression of hip OA is very unpredictable and its natural history remains unclear. This is because osteoarthritic changes may or may not be precursors of hip OA. Thus, not all cases in the pre-radiographic phase progress into end-stage disease. Additionally, a recent systematic review reported that traditional prognostic factors such as age, body mass index and joint space narrowing (JSN) may be associated with incidence of hip OA but do not estimate its progression.⁸ Altogether, due to its non-linear development, lack of comprehensive data and inadequate knowledge of pathophysiological mechanisms, it is difficult to estimate or identify those at higher risk of hip OA.

Detection and Diagnosis

Techniques for assessing hip OA are slowly changing but for now radiographs remain the ‘gold standard’ method for detection of OA. Several atlases have been published which provide comprehensive guidance for assessments of different stages of knee and hip OA.⁷⁶⁻⁷⁸ Radiographic hip OA was first defined by Kellgren and Lawrence (K-L). Table 1-1 describes this simple and basic semi-quantitative method which is still widely used in both clinical and epidemiological studies. Radiographic assessment of hip OA includes assessing femoral or acetabular JSN and osteophytes. JSN (superior and axial) and osteophytes (femoral and acetabular) are traditional hallmark surrogate measures used to assess cartilage loss and disease severity.^{79, 80} While, greater JSN indicates loss of articular cartilage;^{81, 82} osteophytes are bony outgrowths or spurs along the joint margins formed due to abnormal endochondral ossification.¹⁷

Other X-ray based techniques used to measure radiographic hip OA are minimal joint space (MJS) and croft grading system.^{83, 84} The K-L grading system is preferred due to its higher inter-rater reliability and proven proficiency to predict end-stage hip OA⁸⁵ but it is non-linear and insensitive towards changes over time. For radiographic assessment of hip in this thesis; the Osteoarthritis Research Society International (OARSI) grading system based on Altman’s atlas was applied.^{76, 77} This grading system (Table 1-2) includes individual assessment of JSN

and osteophytes on a 4-point scale (grade 0-3). This method allows assessment of radiographic features either separately or altogether (as a total radiographic OA score). This scale was chosen because it is a standardized semi-quantitative technique for assessing radiographic features, has widespread accessibility, validity, and relevance in cross-sectional and longitudinal studies.^{[85](#), [86](#)}

Table 1-1: The Kellgren and Lawrence (K-L) grading system for hip OA

Definition grades		Description
Grade 0	No osteoarthritis	
Grade 1	Doubtful	Possible narrowing of the joint space medially and possible osteophytes around the femoral head; or osteophytes alone.
Grade 2	Mild	Definite narrow of joint space inferiorly, definite osteophyte and slight sclerosis.
Grade 3	Moderate	Marked narrowing with joint space, definite osteophytes, some sclerosis and cyst formation and deformity
Grade 4	Severe	Gross loss of joint space with sclerosis and cysts; marked deformity of the femoral head and acetabulum and large osteophytes.
Hips classified as grade 2 or more were defined as having osteoarthritis. ⁷⁹		

Table 1-2: Individual radiographic features measured by the OARSI atlas for hip OA

Feature	Score
Hip joint space narrowing (JSN)	
Axial	0-3
Superior	0-3
Hip osteophytes	
Superior femoral	0-3
Superior acetabular	0-3

OARSI: Osteoarthritis Research Society International ⁷⁷

Score ranging from 0 to 3 where 0= no disease and 3= most severe disease

The clinical diagnosis of hip OA is based on both radiographic and clinical factors. In comparison to radiographic assessments, the American College of Rheumatology (ACR) classification combines clinical, radiographic and laboratory findings for diagnosis of hip OA. ⁸⁷ This diagnosis is chiefly based on hip pain, along with other symptoms such as changes in joint movement, morning stiffness, age and confirmation by negative laboratory testing. Such methods not only allow diagnosis of hip OA but also provide an opportunity for a differential.

Assessment of pain is highly subjective and its intensity is variable. Thus, pain assessment in OA is a challenging task. Hence, rather than using self-reported questionnaires which, only assess pain as yes or no; comprehensive pain scales that record intensity of pain, severity of disease and impairment of function are preferred. For instance, symptomatic hip OA can be evaluated using a VAS (Visual Analog Score).⁸⁸ However, the hip specific WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index)⁸⁹ or HOOS (Hip disability and Osteoarthritis Outcome Score)⁹⁰ are far more comprehensive scales and mostly preferred in epidemiological studies.

Disadvantages of X-rays

As X-rays are non-invasive and inexpensive they have been extensively used in large population-based studies. Nevertheless, meta-analyses reveal that hip radiographic features relate poorly with significant clinical features such as hip pain and also suggest that radiographic features have low prognostic value. In addition, X-rays provide limited visualization of the joint and are less sensitive to early degenerative changes and/or change in disease status over time.^{8, 75, 91} Due to these flaws, radiological assessments of hip OA could lead to higher measurement error in longitudinal and large multicentre-based clinical trials. Hence, to study temporal progression of hip OA at two or more time points, development of better techniques are required.

Increasing importance of MRI

Recent guidelines for clinical trials strongly recommend using both X-rays and MRI for assessment of OA.⁹² MRI is comparatively superior to conventional radiographs, as it provides high-spatial-resolution, multiplanar imaging, and excellent tissue contrast. MRI

allows a three-dimensional assessment of all the components of the joint along with the cartilage. Despite its exclusive features, only a few studies have used MRI's to examine hip OA. Features including cartilage defects, bone marrow lesions (BMLs) subchondral cysts, paralabral cysts, osteophytes, labrum tears, synovitis, effusion and loose bodies have been used to develop semi-quantitative MRI-based scoring systems for overall evaluation of structural changes in hip OA.^{93, 94} Both, HOAMS (Hip osteoarthritis MRI scoring system) and SHOMRI (Scoring Hip Osteoarthritis with MRI) suggest assessing similar MRI features to evaluate hip OA on MRI. While hip OA features assessed in HOAMS associated with K-L grading system, hip OA features assessed in SHOMRI are associated with clinical parameters, K-L and OARSI radiographic grading systems.^{93, 94} Although the inter-rater reliability of these techniques is high, sensitivity and usefulness of such methods in predicting disease progression still need to be validated in larger studies.

In the next sections of this review, important MRI-based and morphological determinants of early hip OA shall be described.

Bone marrow lesions (BMLs)

Bone marrow is a soft tissue found in the interior of long bones.⁹⁵ It's a compartment that is separated from the joint cavity by a very thin layer of bone and harbors fat cells (adipocytes) and a dense network of trabecular bone.⁹⁶ A collection of immune cells and microvessels in the bone marrow replace the fat cells, leading to an increase of water content. Such inflammatory infiltrates adjacent to the subchondral bone are called bone marrow lesions (BMLs) (Figure 1-1).⁹⁶ BMLs appear as non-specific, irregular areas of low signal intensity on T1 MRI's or as high signal intensity areas on T2 or STIR (Short T1 Inversion Recovery) MRI images.⁹⁷ BMLs are not visible on X-ray, ultrasound (US), computed tomography (CT) or Doppler scans.⁹⁸

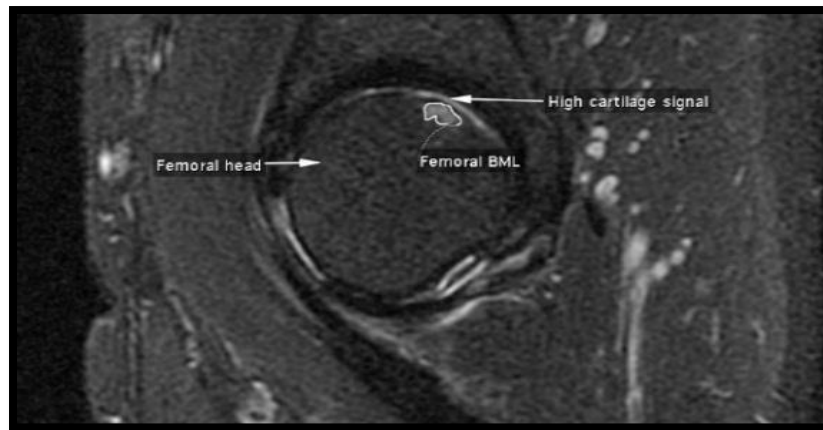


Figure 1-1: An example of hip BML located in the femoral head.

Studies have identified BMLs in subjects with hip osteonecrosis⁹⁹, hip transient osteoporosis⁶⁵ and femoral head stress fracture.¹⁰⁰ In general, the pathophysiology of BMLs is heterogeneous and may very likely differ in different types of musculoskeletal conditions such as injury, tendinitis, osteoporosis, rheumatoid arthritis (RA) and OA.¹⁰¹

Pathology of BMLs

As only a limited number of histological studies have examined BMLs, its pathology remains fragmentary. From what is known, BMLs consists of fibrosis, lymphocytic infiltrates and increased vascularization with mostly a small amount of actual edema. Furthermore, BMLs in OA also contain bone marrow fat necrosis, trabecular fractures and areas of active bone formation/resorption.^{97, 101, 102}

The biochemical profile of BMLs present with some interesting insights. For instance, in a study, biochemical markers such as bone-specific alkaline phosphatase (bone ALP), osteocalcin (OC), procollagen Type 1 N-terminal propeptide (PINP) and C-terminal cross-linking telopeptide (ICTP) were extracted from decompressed femoral heads. In comparison to those without a BML, samples of calcaneus bones with a BML had significantly elevated levels of these biochemical markers.¹⁰³ These results suggest an increase in bone turnover in bone areas with BMLs. In addition, another study demonstrated that angiogenesis factors (formation of new capillary blood vessels) like VEGF and CYR61 were also elevated in bone cores with BMLs.⁹⁷ In summary, BML patterns seen on MRI are most likely driven by elevation of biochemical markers and increased expression of cytokines and angiogenic

factors in the subchondral bone. Thus, presence of a BML adjacent to the subchondral bone may represent a local area of high bone turnover and the presence of such lesions might be a response of the bone towards a disease process.

Significance of hip BMLs in OA

BMLs were first described and identified in 1988 and their association with pain was demonstrated.¹⁰⁴ In OA, the association between BMLs and end stage knee OA was confirmed in 2000.¹⁰⁵ Over the years, several studies have demonstrated that participants with BMLs are at greater risk of worsening knee pain and larger BMLs correlate with higher intensity of knee pain.¹⁰⁶⁻¹⁰⁸ Reports based on longitudinal data present with similar evidence. For instance, increase in BML size was associated with an increase in knee pain while resolving BMLs were associated with a decrease in pain.^{106, 107, 109, 110} Additionally, larger BMLs not only predicted worsening pain but also greater cartilage damage.¹⁰⁸ The current emphasis on BML has increased as BMLs play a crucial role not only as a ‘*pain generator*’ and associate with structural changes in cartilage and subchondral bone from early stages of the disease pathophysiology.⁹⁷ Much is known about knee BMLs, but very less emphasis has been placed on BMLs at other sites, such as the hip.

Hip BMLs were primarily described in MRI’s of twelve subjects with rapidly destructive hip osteoarthritis (RDOA). Hip BMLs along with extensive hip effusion and synovitis were found in MRIs of all the subjects. However, BMLs were not specifically studied.¹⁰² Nevertheless, a subsequent study confirmed that hip BMLs patterns seen on MRI correlate with BMLs found on histopathological examination of the femoral head.¹¹¹ In a study analyzing the role of hip BMLs in sixteen subjects with end-stage hip OA, some interesting primary results were presented. It demonstrated an association between weight bearing focal hip BMLs, hip pain, radiographic features and most of all micro-fractures in the subchondral bone.¹⁰¹ Subsequently, some preliminary research on hip BMLs has been carried out in a small set of MRI studies. Two of such studies focused on developing standardized scoring systems for hip OA which included hip BMLs. While these studies found no or modest correlations of hip BMLs with pain and other symptoms;^{93, 94} a small case-control study demonstrated that hip BMLs were not only associated with hip pain but also hip cartilage defects, particularly acetabular cartilage defects.¹¹² These histopathological and semi-

quantitative assessments of hip BMLs present with little evidence and there are no longitudinal or prospective population-based studies on hip BMLs.

We know that knee BMLs play a far more extensive role; as these are transient and an increase or decrease in knee BML size may influence knee pain,¹⁰⁶ knee structure^{113, 114} and also elevate the risk of subsequent knee joint replacement.^{107, 113} To make matters worse, BMLs due to their location and composition may cause bone demineralization, in turn affecting bone architecture rendering it vulnerable towards attrition.^{63, 106, 114, 115} And yet, the natural history of hip BMLs remains unexplored. Furthermore, existing data on hip BMLs is not generalizable and hardly puts any emphasis on the actual role of hip BMLs in the progression of hip OA.

The interactive role of hip BMLs makes it a potential target for treatment of hip OA. Given the deficiencies in the data, studies describing the actual role of hip BMLs and exploring its pathophysiology may lay a foundation for future clinical trials. Thus, chapters 4 and 5 of this thesis focus on the associations of hip BMLs in a population-based cohort.

Cartilage and OA

Cartilage is a non-vascular structure found in various parts of the body, but articular cartilage is a type of hyaline cartilage specifically found on the joint surface. The hyaline articular cartilage is an alymphatic, aneural and avascular tissue predominately made up of ECM with chondrocytes. As it's avascular it depends on synovial fluid and subchondral bone for nourishment.¹¹⁶ The cartilage is made up of four layers (zones) and each has its own distinct matrix as seen in Figure 1-2.¹¹⁷ The overall tensile meshwork of cartilage and its strength is due to its primary composition of ECM, type II collagen and PG (proteoglycan) Aggrecan.¹¹⁸

Due to such properties, the cartilage can provide a frictionless surface for bones and plays a vital role in joint loading.¹¹⁹ The function of chondrocytes is to maintain the ECM, but these can be influenced by growth factors (GF), cytokines, adipokines, inflammatory mediators and matrix fragments leading to breakdown of the ECM.¹²⁰ Also, deep and superficial lacerations (defects) in the cartilage, due to disease pathology or injury, can affect the ECM. Moreover, in OA the inflow of water increases into the cartilage (probably through defects) compromises its integrity and thus increases its susceptibility towards injury. Unfortunately,

due to its avascular nature and lack of stem cells, the cartilage is difficult to regenerate or repair.¹²¹

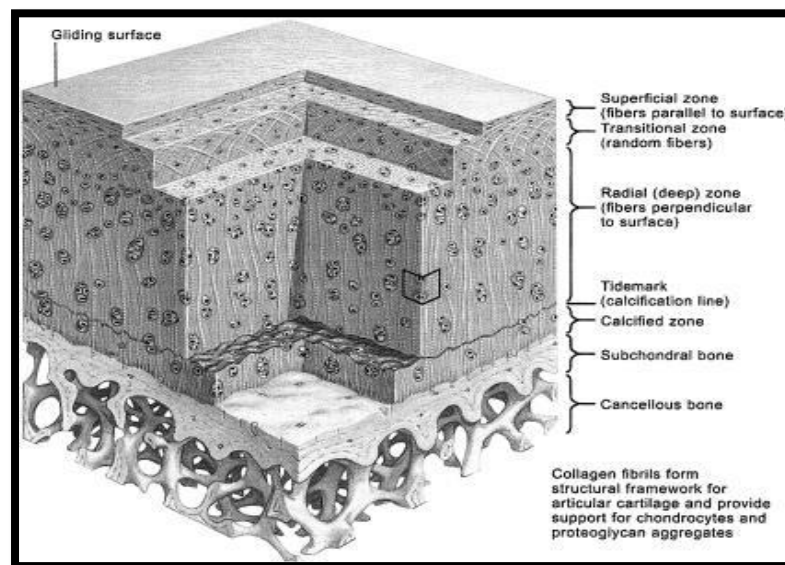


Figure 1-2: Structure of the articular cartilage. Reproduced from Carry-Beth *et.al*¹⁰⁵

Hip cartilage and high cartilage signal

Due to the significance of joint cartilage, research involving cartilage morphology is in high demand.⁸¹ MRI has been widely used to calculate cartilage volume and assess structural damage in knees with and without OA. Some cross-sectional studies have utilized T2 MRI images to evaluate hip cartilage volume⁸¹ but measuring cartilage volume at the hip is a challenging task due to its three-dimensional shape and thin cartilage. Additionally, assessment of cartilage volume in longitudinal studies is susceptible towards measurement error due to a high CV (coefficient of variation). In OA, the idea behind measuring cartilage volume is to track and analyze changes in cartilage health, but for this purpose, other imaging predictors or techniques can also be applied.

High signal intensity change is described as a variation in the signal intensity of the articular cartilage. It represents a break in any part of the hyaline cartilage through which water leaks

inside the cartilage and appears as a bright band visible on MRI (Figure 1-3).^{122, 123} This feature is visible in early stages of OA, however, in the later stages when articular cartilage may be replaced by fibrocartilage this signal might decrease or may not be visible on MRI.¹²² Due to its characteristics it has been proposed that high cartilage signal can be a good predictor for estimating cartilage health.¹²⁴

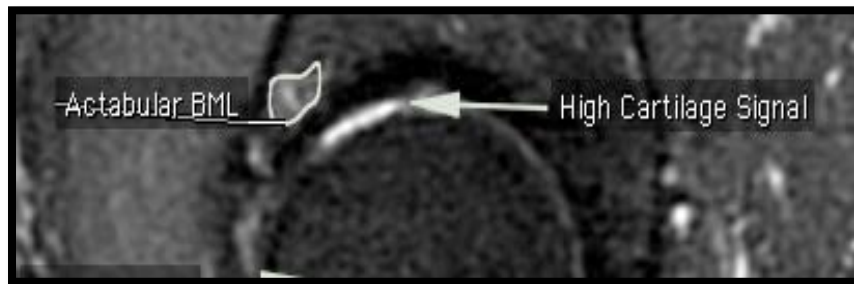


Figure 1-3: Presence of high cartilage signal and acetabular BML on a STIR MRI of the hip.

Significance of high cartilage signal in hip OA

In OA, high cartilage signal forms a part of the classification system for measuring changes in cartilage morphology of the knee.^{125, 126} For the hip, it was first mentioned in a small prospective study of eighteen subjects with the objective of developing a grading system to assess the severity of hip OA,¹²² but the authors did not describe correlations of cartilage signal. Nevertheless, in a second study, a decrease or increase in hip cartilage signal intensity was recorded and it was correlated with cartilage integrity. However, change in signal was not associated with pain.¹²³ Cartilage is aneural and the presence of cartilage signal intensity is an indicator of cartilage breakdown.¹²⁷ Therefore, it's less likely to be associated with pain. However, this concept needs further consideration, as one study reported associations between cartilage signal change and knee pain.¹²⁸ Newer studies describing MRI-based scoring systems for grading hip OA have not included this feature in the classification system^{93, 94} and instead describe changes in cartilage from grade 0-3 beginning with <25% cartilage damage. In general, change in cartilage signal intensity may be a useful predictor of cartilage integrity and features of this predictor can be confirmed by examining its associations with other characteristics of OA.

Significance of cartilage defects in hip OA

Cartilage is a three-dimensional tissue with unique morphological features and biomechanical properties, and it is best visualised on MRI.¹²⁹ Cartilage defects are superficial or deep breaches in articular cartilage that ultimately lead to ulceration of the subchondral bone. These generally start off as '*micro defects*' or small cracks in the joint cartilage that widen over time.¹³⁰

The significance of cartilage in OA is now being debated; as many researchers suggest that other features of the joint need equal attention. The reason cartilage remains in the '*limelight*' is because the joint depends on articular cartilage for smooth functioning and any change in joint structure due to extrinsic or systemic factors have a direct impact on the cartilage.¹⁷ For example, MRI-based studies have shown that structural changes in the knee joint due to injury (joint/ligaments),^{49, 131} meniscal tears,^{132, 133} knee BMLs^{107, 114} and knee effusion-synovitis¹³⁴ have a direct impact on the knee cartilage and encourages formation of knee cartilage defects and/or cartilage degradation.

Even though cartilage is the susceptible target in incidence and progression of OA, apart from knee cartilage, in-depth examination of cartilage at other sites, including the hip has not been conducted. Hip cartilage defects were reported in asymptomatic young and elderly subjects,¹²³ in those with RDOA¹⁰² and histopathological examinations of the femoral head of subjects with end-stage hip OA.¹⁰¹ However, these small cross-sectional studies did not report correlations of hip cartilage defects. In the last few years, there has been some development in research involving hip cartilage defects. For example, in a few small recently published MRI-based studies, hip cartilage defects was associated with radiographic hip OA, hip pain and hip BMLs.^{93, 112, 135} Also, hip cartilage defects are associated with lower hip cartilage volume¹³⁶ and obesity.¹³⁷ However, no in-depth or longitudinal investigations based on hip cartilage defects have been carried out.

Cartilage is non-restorable and as yet, no man-made material can replace it. Developing preventive or therapeutic techniques for hip OA could rely on decoding the pathophysiology of hip cartilage defects. However, the present data on hip cartilage defects is sketchy and comprehensive research or data describing the impact of hip structural abnormalities on hip

cartilage does not exist. Additionally, there are very few clinical trials or population-based studies examining changes in at hip cartilage. New techniques such as cartilage regeneration remain experimental, and there is no certainty that replacing the cartilage would halt the development of the disease. Thus, methods for repairing/restoring cartilage in OA may not be successful due to lack of information. Accordingly, chapter 5 of this thesis aims to identify the interactions of hip cartilage defects with clinical, demographical, structural and radiographic changes in older adults.

Synovitis-effusion

Synovial fluid (SF) is a viscous, straw-colored fluid present in cavities of synovial joints such as the hip and knee (Figure 1-4). The major source of SF is the synovial membrane (SM) which also nourishes the cartilage.¹¹⁶ SF has several biomechanical, metabolic and regulatory functions.¹³⁸ One of its primary functions is to lubricate joint cartilage along with reducing friction. SF consists of two important components lubricin and hyaluronic acid (HA).^{116, 138} These components are responsible for joint lubrication and also maintain the integrity of articular cartilage. Along with this, SM is responsible for removal of metabolites and products of matrix degeneration.^{116, 139}

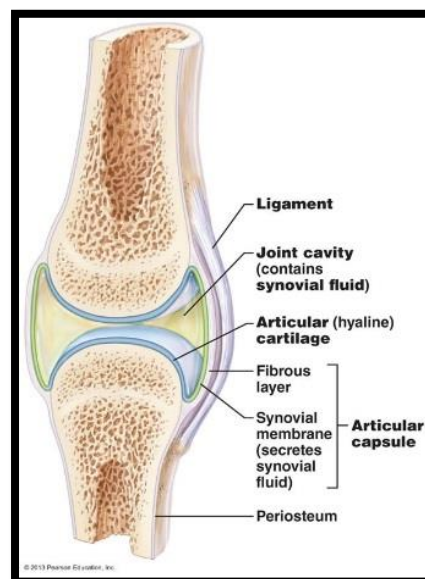


Figure 1-4: Typical synovial joint (available and reproduced from the public domain).

URL: <http://study.com/academy/lesson/what-is-synovial-fluid-definition-function.html>

SM inflammation occurs in OA, but it may not be the dominant driving force. However, synovitis-effusion is one of the factors in OA pathophysiology which contributes to higher joint pain and reduction of joint function.¹⁷ Additionally, at any stage of OA or other diseases, inflammation of the SM alters the composition and function of the SF, which in turn has an adverse effect on cartilage and surrounding joint tissue.¹³⁹ Joint effusion can be visually distinguished from synovitis using contrast-enhanced gadolinium injection, but this technique is not commonly used due to potential side effects and high cost. Recently, the term effusion-synovitis has been proposed for effusion and synovitis because these two features cannot be differentiated by non-contrast MRI.

Significance of hip effusion-synovitis in hip OA

In regards to OA, the significance of synovial membrane is high due to its link with cartilage, joint structure, and clinical symptoms. Although, OA is not traditionally considered an inflammatory type of arthritis, ‘pain flares’ in OA subjects are common.^{115, 140} In addition, studies have revealed that inflammatory markers such as CRP (C-reactive protein) and TNF- α (tumor necrosis factor- α) associate with knee pain, knee ROA and cartilage loss.^{141, 142}

Joint effusion can be visually distinguished from synovitis using contrast-enhanced gadolinium injection, but this technique is not commonly used due to potential side effects and high cost. Recently, the term effusion-synovitis has to be proposed for effusion and synovitis because these two features cannot be differentiated by non-contrast MRI.¹⁴³ Clinical examination of effusion-synovitis is challenging, especially in deep joints like the hip,¹³⁹ and MRI and US are the best non-invasive techniques to examine hip effusion-synovitis. Several types of studies, including MRI-based, have reported associations of knee joint effusion-synovitis proving that it is one of the causes of knee pain, has an adverse effect on cartilage and is linked with radiographic knee OA.^{115, 134, 144-146} However, at the hip, limited literature exists and the current data is inconsistent.

Hip effusion and synovitis were assessed individually and reported in those with RDOA and end stage hip OA. However, these studies did not describe the associations of hip effusion or synovitis.^{101, 102} A clinical based studied hip effusion-synovitis using US, and revealed that hip effusion-synovitis greater than 9 mm was associated with higher hip pain and severe hip

Radiological OA (ROA).¹⁴⁷ On the other hand, a small subsequent retrospective study found no association between hip effusion and hip pain¹⁴⁸. The results from subsequent two MRI-based studies were also controversial. The first study reported that grade 1 but not grade 2 synovitis was associated with hip pain, but hip effusion did not show any such associations.⁹³ In the second study, no relationship between hip effusion-synovitis and hip pain was found.⁹⁴ It should be noted that the primary goal of these investigations was to validate a scoring system. However, in both studies, effusion and synovitis (assessed together or individually) were associated with severe hip ROA, but other correlates were not investigated. These differences in data could heavily rely on the sample population, disease severity and methods used to assess hip effusion-synovitis, and there is a need for further studies.

Effusion-synovitis may be associated with hip ROA and only one study reports its association with hip pain. Given the impact of effusion-synovitis on the joint and lack of data, MRI-based studies on hip effusion-synovitis are necessary. Data generated by such studies could be very beneficial in designing interventions targeting effusion-synovitis, which could in turn aid in controlling OA and preserving cartilage. Thus, chapter 6 in this thesis is the first population-based longitudinal study describing the correlates of hip effusion.

Bone and muscles

Muscles are responsible for smooth joint movements through muscle contractions and relaxations. Along with the joint capsule and ligaments, muscles are also accountable for joint stability and also contribute to physiological strength.¹⁴⁹ Muscles insert into the bone and are further interlinked to the skeletal system by a dense network of nerves and vessels. Hence, a constant strain caused by muscles encourages bone remodeling because the bone is a dynamic tissue that is designed to meet mechanical demands.⁶⁶ Along with the mechanical aspect, muscle-bone interlink is influenced by factors such as genetics, environment, lifestyle, hormones and pathology.¹⁵⁰ Joint stability, especially of the lower limb, is important for high quality of life in those with chronic musculoskeletal disorders. OA is now considered a disease of the whole joint, and there is considerable loss of muscle mass and function in those with OA.^{17, 151} Thus, it has been suggested that along with structural assessment, a focus on muscle health is essential for subjects with OA.^{66, 152}

Significance of muscles in hip OA

Although the role of muscle is well known, its importance in OA has escalated recently as researchers and clinicians have started weighing the impact of physical activity on bone and cartilage.^{153, 154} Muscle health can be assessed in several ways and the simplest method is to use dual-energy x-ray absorptiometry (DXA). DXA calculates skeletal muscle mass, along with lean and fat mass. DXA has been used in several studies to describe the correlations between sarcopenia (loss of muscle mass) and changes in bone in those with OA.¹⁵⁵⁻¹⁵⁷ Nonetheless, to study the physiological or anatomical effect of OA pathology on muscles, MRI and CT scans are superior to DXA because these imaging techniques can be used to visualize, quantify and assess muscles individually. Also, instead of measuring the entire muscle volume, a validated and surrogate measure termed muscle cross-sectional area (CSA) (Figure 1-5) is preferred.¹⁵⁸

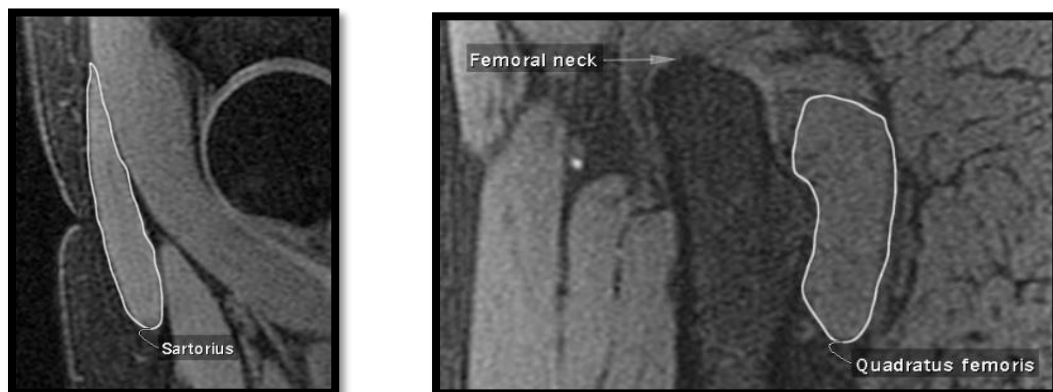


Figure 1-5: An example of assessment of hip muscle CSA (Sartorius and quadratus femoris) using T1 MRI images. Images obtained from TASOAC study.

Although muscles are identified as important determinants of OA progression, only a handful of muscles have been studied. In a pain-free community-based study, vastus medialis and lateralis muscle CSA was positively associated with patellar cartilage and bone volume,¹⁵⁹ but in those with patellofemoral pain, there was a reduction in quadriceps muscle CSA.¹⁶⁰ Hence, OA pathology influences changes in muscle CSA. Joint pathology at one site, especially at the hip may affect muscles of the lower limb. For instance, in twenty-two subjects with and without hip OA, reduction in muscle CSA was not only seen in muscles of hip such as gluteus but also in muscles of the knee such as vast and hamstrings.¹⁶¹ In

addition, in a study including eighteen women and four men with end-stage hip OA; atrophy of the hip, knee, calf and ankle muscle CSA was reported. Nevertheless, after total hip replacement (THR) or removal of joint pathology, all these muscles regenerated to a certain extent.¹⁶² This outcome could be due to the reduction of pain and/or improvement in joint biomechanics. However, it's unknown if these subjects underwent rehabilitation and there have been no subsequent studies following up these results.

Muscle atrophy could be an indicator of changes in bone density because studies show that larger muscle CSA correlates with better bone structure and size.¹⁵¹ Changes in BMD are plausible in those with OA and maintaining muscle might be helpful but this concept has been sparsely studied. A small clinical trial based on post-menopausal women proposed that muscles involved in major skeletal movements, which insert into the bone and were local to the '*affected joint*' might be worth targeting during rehabilitation for the preservation of local bone density.¹⁶³ This might be very true because another study demonstrated that deconditioning of the hip joint (joint unloading) resulted in a decrease in bone density and muscle CSA.¹⁶⁴

Alterations in BMD may not be an apparent symptom, but a loss in muscle strength due to muscle atrophy is a clear indication of loss in joint function in subjects with OA. Muscles are one of the main *force generators* and muscle strength and CSA vary with age and lifestyle.¹⁶⁵ For instance, in young athletes gluteal muscles were found to be strongly correlated with muscle strength, but in the elderly, quadriceps muscle CSA was correlated with knee extension strength during sit-to-stand testing.^{166, 167} The inter-relationship of muscle CSA and strength also relies on joint loading and muscle recruitment¹⁶⁸ but not all muscles have identical intrinsic strength. For example, amongst young soccer players, the correlation of CSA of gluteus maximus with muscle strength was stronger in comparison to iliopsoas muscle CSA.¹⁶⁶ This could rely on both joint loading and recruitment of muscle during activity. With aging and muscle infiltration due to excess adiposity, muscles such as proximal gluteal muscle may become weak leading to lower muscle strength and joint stability.¹⁶⁹

Muscle atrophy in OA could be a result of joint disuse, pathology or pain. Furthermore, muscle atrophy is one of the causes of further bone loss and it also causes a reduction in muscle strength, which affects the gait and in turn, daily activities. Yet, regardless of the

importance of muscles, the studies discussed above are small and have examined either one or two muscles. Additionally, most of them have not been conducted at the hip and the overall data is not generalizable. A study of hip muscle morphology and its associations with bone density and muscle strength could be a great addition to the literature and could provide a better insight into these aspects, especially in an older population (chapter 8).

Bone shape and progression of OA

End stage OA leads to deformation of the bone with severe cartilage damage and destruction of the surrounding joint tissue.¹⁰¹ Such changes are accompanied by thickening of the subchondral bone plate, higher bone mineral density (BMD), bone stiffness and change in the bone trabecular structure.¹⁷⁰ It's unknown when or how these changes are triggered, but these have a starting point which could determine the severity of the disease. As discussed earlier, hip OA is heterogeneous and not every case requires a THR. The severity of hip OA depends on the intensity of its progression and number of risk factors that an individual is exposed to. In addition, there is no known way to monitor or track the progress of hip OA because radiographs are insensitive to minor changes and frequent MRI's may not be feasible.

Gross geometrical measures have been applied to predict incidence and prevalence of hip OA and anatomical malformations of the hip.^{171, 172} Hip geometry has been vastly studied by using validated geometrical measures such as centre-edge angle or Wiberg angle, triangular index, hip-axis-length, femoral-neck-width etc. These geometrical measures have been used to predict hip-related anatomical malformations such as pistol grip deformity and femoroacetabular impingement in large population-based cohorts.^{172, 173} However, these are less sensitive to change, are liable towards higher measurement errors and do not provide a global assessment of bone. Thus, perhaps it's time to shift our attention from the use of non-linear semi-quantitative measurements to semi-automatic measurements, especially for three-dimensional joints like the hip.^{174, 175}

Quantification of small and large variants in the bone morphology can be achieved by using software such as active shape modeling (ASM).¹⁷⁴ ASM is an imaging tool which is widely used from face recognition to medical imaging.¹⁷⁴ Overall, ASM is a method of analyzing differences in patterns of bone shape that have inherent variability. In ASM, radiographs, DXA and MRI images can be used to build semi-automatic computerized statistical models.

The ASM is used to build a Statistical Shape Model (SSM) using points that are placed around selected anatomical features (Figure 1-6). The ASM software then generates distinct hip shapes or modes of variations across the entire cohort. Each mode is a descriptor of change in hip shape a number of standard deviations (SD) away from the average shape of the entire cohort.¹⁷⁶ All shape modes are independent of each other. Such quantitative assessments techniques have been used in studies to assess the shape of the knee¹⁷⁷, spine¹⁷⁸,¹⁷⁹ and foot¹⁸⁰. SSM can be applied to measure proximal femur shape and this method has several advantages over traditional geometric measurements as it captures a global bone shape rather than a limited subset of components of that shape.¹⁸¹

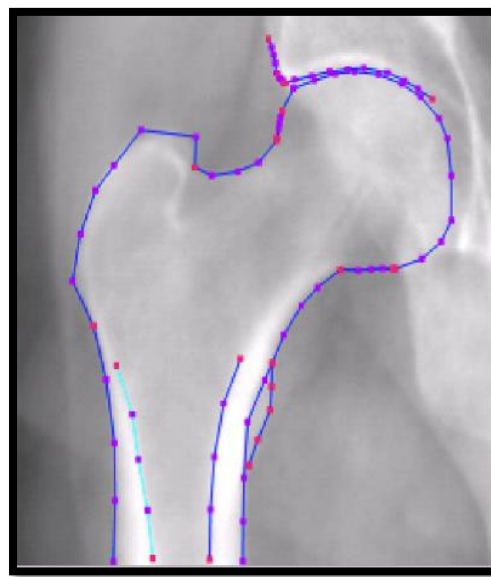


Figure 1-6: Application of SSM to study hip shape.

Image from the TASOAC study

ASM is semi-automated computerized technique and easily reproducible. For instance, in a study using ASM models to investigate different shapes of the hip, the point to point variability between two observers (distance between a points coordinates when placed by each observer) has been reported as good as 1.3mm.¹⁷⁵ In a subsequent study, ASM was used to assess spine on MRI images, and inter and intra-observer reliability was between 0.98-1.00. In the same study, the relative error in the shape models was reported between 4-9%, much lower than conventional measurements.¹⁷⁹

Significance of bone shape in hip OA

In hip OA, SSM was first used to assess hips of one hundred and ten subjects with no radiographic hip OA at baseline. Three peculiar shapes of the hip (modes) at baseline projected incidence and severity of hip OA at the end of six years of follow-up. For instance, the sharp transition of the femoral head into the upper femoral neck (mode 3) or lower femoral neck (mode 6) at baseline was linked with a greater probability of development hip OA at follow-up. ¹⁷⁰ In a subsequent study, shape variations in the femoral head and neck, along with anatomical disproportions in the proximal femoral head were significant in predicting the two-fold risk of hip OA. Such disproportions included a larger femoral head in comparison to rest of the hip joint. ¹⁸²

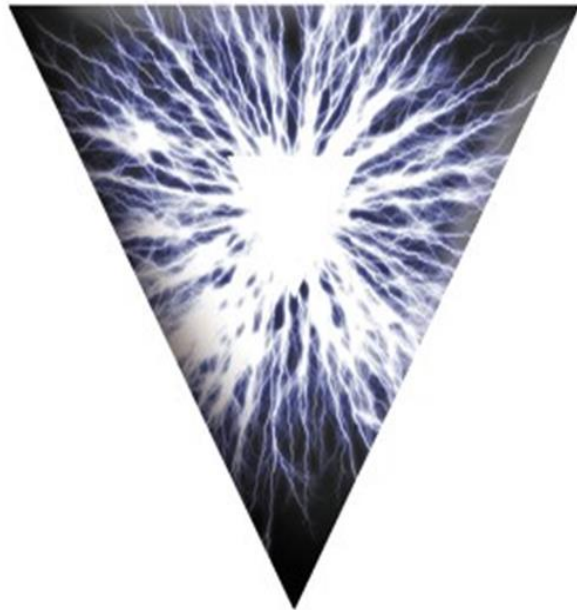
These studies used plain radiographs to conduct hip measurements, but DXA images which are two-dimensional images generated by a three-dimensional scanner can also be used in ASM. In an SSM model of the femoral head which also included the acetabulum; it was demonstrated that changes in bone density and position of the femoral head in the acetabulum predicted a higher risk of hip pain. In this study, the shape modes that associated with clinical features did not associate with radiological features and vice versa. ¹⁸³ It could be assumed that the link of hip shape variations may be stronger with structural changes than clinical symptoms. ¹⁸⁴ Thus, different hip shapes may predict either clinical or radiological elements of hip OA.

SSM, due to its accuracy and sensitivity, can be applied in monitoring and predicting hips at greater risk. SSM is being updated and tested to be used in the clinical field such as planning orthopedic surgeries. ¹⁸⁵ The application of SSM needs to be assessed further, especially in a large community-based population. SSM has the ability to identify hip shapes that predict hip OA or hip shapes that are protective against the development of hip OA. Studies based on this concept could have a dual outcome. Firstly, SSM can be used to monitor or track patterns of progression of hip OA and secondly it could help us understand the mechanisms behind these subtle bone changes.

Summary

Prevalence of OA is high and with increasing age and obesity rates, its pace is estimated to grow in the near future. Today, a vast knowledge of OA exists but it's mostly focused at the knee. OA of the hip is one of the major causes of disability and joint surgery in older adults, and yet only a few studies have focused on investigating its natural history. Evidence suggests that well known traditional prognostic factors of hip OA such as age and JSN may not be helpful in estimating the severity of the disease. Thus, there is a need for newer larger population-based studies to investigate the roles of BMLs, change in cartilage signal intensity, cartilage defects, effusion-synovitis, bone shape and muscles at the hip. These imaging biomarkers may not only be linked with clinical and radiographic OA but also with changes in the subchondral bone. Such studies could lay foundations for future research and help in identifying therapeutic targets for developing disease-modifying drugs for those suffering from OA.

Chapter 2 Research questions



Research questions

The aim of this thesis is to study the hip as a whole joint and to describe the associations of major risk factors which might be involved in the pathogenesis of hip OA and if possible explain the conceivable mechanisms.

Each chapter of this thesis attempts to describe one research question which then contributes towards the overall aim of the thesis

Research questions:

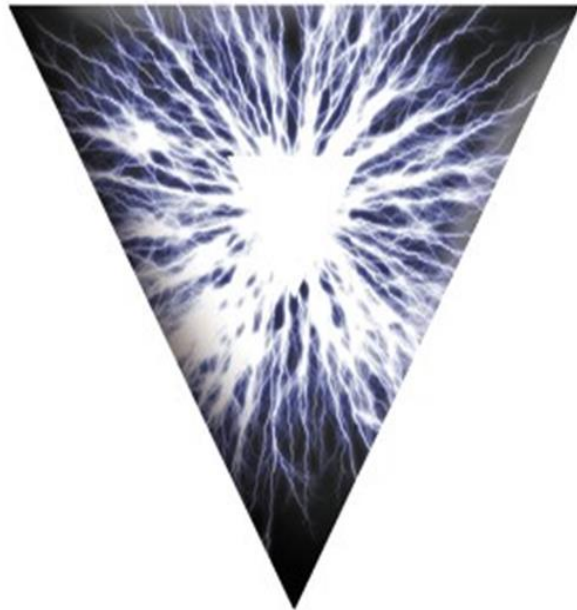
- 1) What are the cross-sectional and longitudinal associations between hip BMLs, hip and knee pain? Also, does change in hip cartilage signal associate with hip pain and hip BMLs?
- 2) Are hip BMLs associated with hip, femoral neck and spine BMD?
- 3) What are the associations of hip cartilage defects with hip pain, muscle strength, physical activity, hip BMLs, high cartilage signal, hip effusion-synovitis and hip ROA?
- 4) Does hip effusion-synovitis associate cross-sectionally and longitudinal with hip pain, hip BMLs, hip cartilage defects and radiological hip OA?
- 5) What are the cross-sectional associations between hip muscle CSA, muscle strength, and BMD of the total hip, femoral neck and spine?
- 6) Hip shape, how does it relate to clinical features, structural and radiological changes in older adults with early hip OA?

Key hypothesis

- 1) Standardized and reproducible methods can be developed to assess hip structural changes (BMLs, defects, and effusion-synovitis), hip muscles and hip shape using hip MRI and DXA images.
- 2) Changes in hip structure, muscles and hip shape are associated with clinical, demographical, subchondral bone changes and radiographic factors relevant for the pathophysiology of early hip OA.

- 3) Structural changes at the hip might be co-dependent on each other, and have a causal link relevant to the pathogenesis of early hip OA.

Chapter 3 Materials and methods



Preface

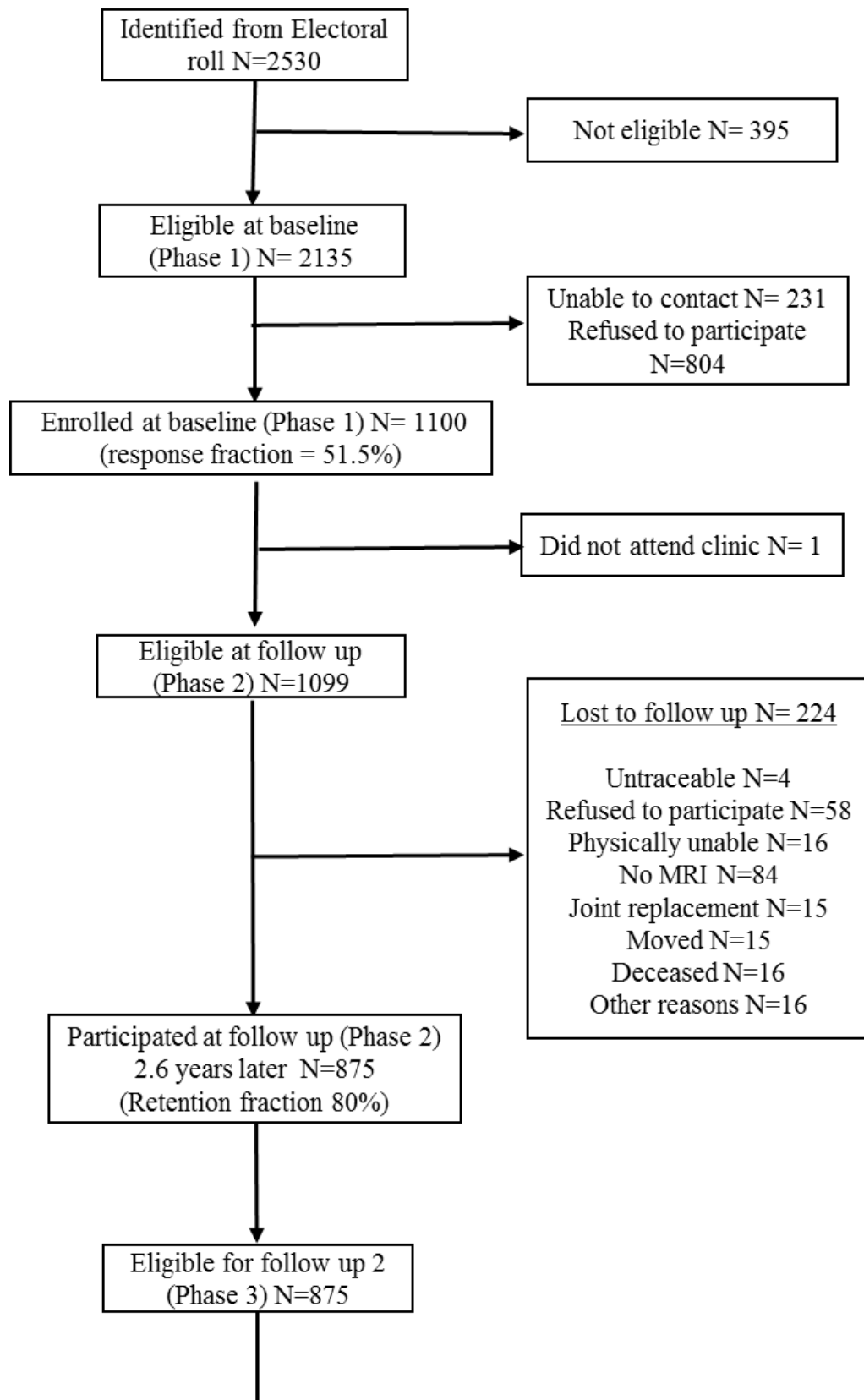
The research reported in this thesis is based on the data collected on participants in the Tasmanian Older Adult Cohort (TASOAC). This chapter describes the TASOAC study and its design, and provides an outline of the protocols of measurement that were used. Further specific details are provided in each chapter.

Subjects

The TASOAC study is a prospective, population-based study that was initiated in 2002. The goal of this study was to identify the environmental, genetic and biochemical factors associated with the development and progression of OA at multiple sites including the hand, knee, hip and spine. Using a sex-stratified random sampling technique, older adults between the ages 50-80 years were selected from the state electoral roll for Southern Tasmania (population 229,000). Electoral rolls represent a complete listing of Australian residents that is available because voting in state and federal elections is compulsory and, the coverage of the population is comprehensive. The sample was stratified by sex to provide an equal number of men and women in Southern Tasmania. The TASOAC study was designed to cover community-dwelling older adults and institutionalized older adults were excluded. Additionally, as MRI was a requirement to assess OA progression, participants were excluded if they reported any contraindication for magnetic resonance imaging (MRI).

Figure 3-1 provides an overview of the recruitment of study participants. Of the 2135 eligible participants, 1100 were enrolled in the study, and 1,099 attended a baseline (Phase 1) clinic between March 2002 and September 2004. The overall response proportion was 51.5%. Follow-up data (Phase 2) was collected for 875 participants at a clinic 2.6 years later, and then again for 769 participants (Phase 3) at a clinic approximately 2.3 years after Phase 2. A third follow-up (Phase 4) was conducted for 568 participants at a clinic approximately 5 years after Phase 3.

The sub-sample analysed in this thesis included those who had a hip MRI scan at Phase 2 (n=228) and/or Phase 3 (n=215). The MRI images from Phase 2 and Phase 3 were used in all the studies reported in this thesis other than the final study (Chapter 9), for which DXA images were used.



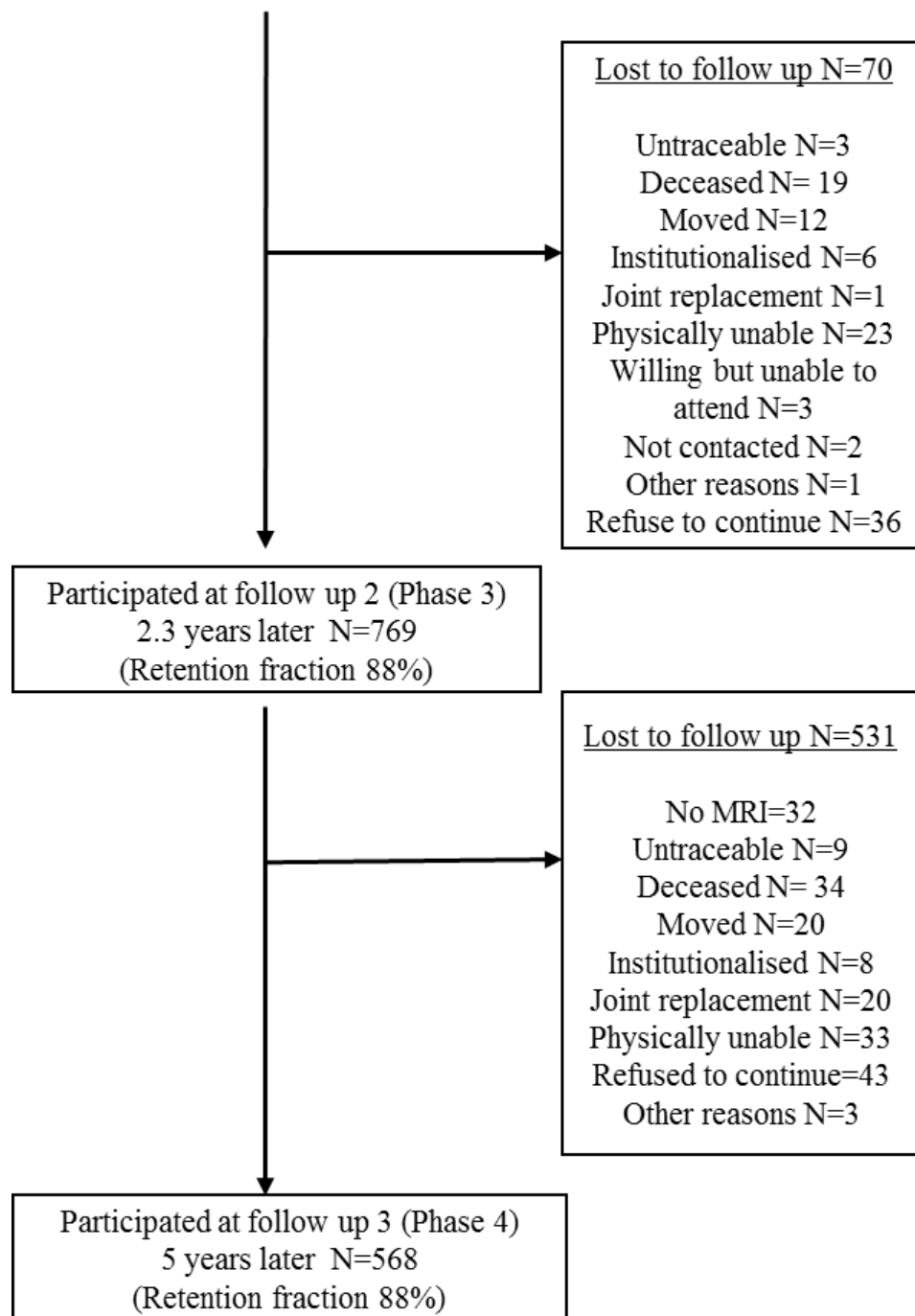


Figure 3-1: Flow chart of TASSOAC study
describing recruitment and participation from phase 1 to phase 3

Measurements

Anthropometrics

Demographic characteristics, medical history and lifestyle factors were assessed by self-administered questionnaires. Weight was measured to the nearest 0.1kg with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707, Hamburg, Germany). Height was measured to the nearest 0.1cm using a stadiometer (with shoes, socks and bulky clothes removed). Body mass index (BMI) was calculated.

Clinical measures

Hip and knee-specific Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index pain score was assessed for each subject. Physical activity and muscle strength was calculated using pedometers and dynamometer. BMD was calculated using DXA scans and radiographic hip OA (ROA) was assessed using X-rays. These measures and their relevant methods of assessments have been described in details in the relevant chapters of this thesis. Examples of hip and knee WOMAC and pedometer diaries have been included in the appendices I-IV.

Magnetic Resonance Imaging (MRI)

For those with a hip MRI, the right hip was imaged in the sagittal plane using a 1.5 Telsa G.E signal whole-body magnetic resonance unit with a phased-array flex coil. Two types of MRI sequences were used.

T1-weighted sequence

Details of the sequence are as follows: T1-weighted fat-suppressed 3-dimensional gradient-recalled acquisition in the steady state; flip angle 55 degrees; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512 x 512–pixel matrix; acquisition time 11 mins 56 s, and one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm with an in-plane resolution of 0.39 x 0.39 mm (512 x 512 pixels).

STIR (Short T1 inversion recovery)-weighted sequence

Details of the sequence are as follows: STIR-weighted, fat saturation two-dimensional fast spin echo sequence; repetition time 4340 ms, echo time 28.4 ms; field of view 20 cm; 15 partitions (16 slides) and 512 x 512-pixel matrix. Sagittal images were obtained at a slice thickness of 3.5 mm with an inter slice gap of 1.5mm.

OsiriX imaging software

All MRI-related semi-quantitative and quantitative measurements were conducted using OsiriX software (University of Geneva, Geneva, Switzerland). OsiriX is imaging software (32-bit Mac version) that allows DICOM images generated by MRI to be uploaded and visualized in multiple planes. This software allows visualization of both bony and muscular aspects of the joint.

Measurement of hip BMLs

Subchondral hip BMLs were quantitatively assessed on STIR-weighted MRI images using OsiriX. BMLs were identified as irregular areas of increased signal intensity adjacent to the subchondral bone on the femoral head and/or the acetabulum. Once the BML was identified, the observer (HA) selected the MRI slice with the largest BML. To quantitatively assess the BML size, contours were drawn around the outer edges of the lesion (Figure 3-2a). The maximum cross-sectional area (CSA) of the hip BML was recorded in cm². The BML was classified as a femoral BML if present in the femoral head, or as an acetabular BML if present in the acetabulum. If more than one BML was present at either site, the size of the larger BML was recorded. In a reliability study (n=25) with re-measurement of BMLs after two weeks, the intra-class correlation coefficient (ICC 1,3) for hip BML CSA was 0.98.

High Cartilage Signal

The presence of high cartilage signal at the hip joint was defined as high signal intensity band within the cartilage either adjacent to the hip BML or at any location on the MRI slice if there was no BML. High cartilage signal was measured semi-quantitatively on STIR MRI images and was graded as 0 for absent and 1 for present (Figure 3-2a). These were measured together

with hip BMLs by the same observer (HA). In a reliability study (n=25), the intra-rater agreement (kappa) for presence of high cartilage signal was 0.88.

Hip cartilage defects

Hip cartilage defects were identified as any change in the hip cartilage at either the femoral or acetabular site. Hip cartilage defects were assessed on STIR MRI images. The scoring algorithm was an adaptation of previously-used semi-quantitative methods for knee cartilage^{107, 126}. Hip cartilage defects were categorized as follows: grade 0 = normal hip cartilage, grade 1= focal blistering or irregularities on the hip cartilage surface or a partial thickness defect, and grade 2= full-thickness hip cartilage defect with bone ulceration and/or exposure of bone. If a hip cartilage defect was located at the femoral head, it was labelled as femoral cartilage defect and if a hip cartilage defect was located at the acetabulum it was labelled as acetabular cartilage defect. If more than one hip cartilage defect was present at one site, the highest score was used. Assessment of hip cartilage has been demonstrated in Figure 3-2b. All the measurements were carried out by one observer (HA). In a reliability study of 40 subjects with re-measurements after four weeks, the intra-rater agreement (kappa) was 0.89.¹⁸⁶

Quantitative assessment of hip effusion-synovitis

Hip effusion-synovitis was assessed as presence of intra-articular fluid-equivalent signal on sagittal STIR MRI. The MRI sequence used to examine hip effusion-synovitis did not allow separation of physiological and pathological effusion. The observer (HA) selected the MRI slice with the largest effusion-synovitis and the maximum CSA of hip effusion-synovitis was assessed and recorded (Figure 3-2c). If the effusion-synovitis was present in more than one site around the femoral head (anterior, posterior or both), then the largest CSA of effusion-synovitis on each site was measured. In the reliability study of 40 subjects with re-measurements after four weeks, the intra-rater agreement (kappa) for presence of hip effusion-synovitis was 0.84, and the ICC (3, 1) for hip effusion-synovitis CSA was 0.97.

Measurement of muscle cross-sectional area (CSA)

Hip muscles were identified within the MRI field of view as shown in Figure 3-2. Measurements of muscle CSA, of clearly defined muscles for which the entire area of the muscle was visible and distinguishable from any adjacent muscles, were made at the anatomical landmarks described in Chapter 8. Muscle CSA (cm²) of eight hip muscles gluteus maximus, obturator externus, Gemelli (superior and inferior), quadratus femoris, piriformis, pectineus, sartorius and iliopsoas was assessed. Figure 2d demonstrates assessment of iliopsoas hip muscle CSA. The CSA of each muscle was measured on two consecutive slices by the observer (HA) and the average was used as the final measurement. If any of the hip muscles were not distinguishable from adjacent muscles, they were not measured; hence, not all eight muscles were measured for all subjects. All hip muscles, except iliopsoas, were measured on sagittal MRI images. For better visualization, iliopsoas was measured by reformatting the whole sagittal plane into an axial plane. In a reliability study of 40 subjects with re-measurements after two weeks, the ICC (3, 1) for hip muscle CSA ranged from 0.98 to 0.99.

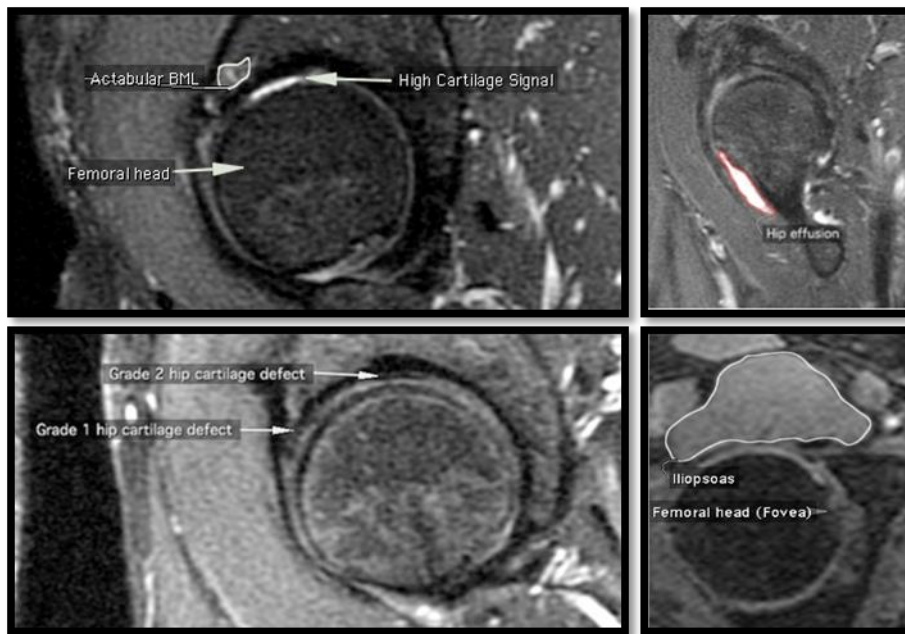


Figure 3-2: Methods for assessment of MRI-related hip features.

- a) acetabular BML CSA and high cartilage signal. b) Categories of hip cartilage defects. c) Hip effusion-synovitis CSA. d) Hip muscle (iliopsoas) CSA.

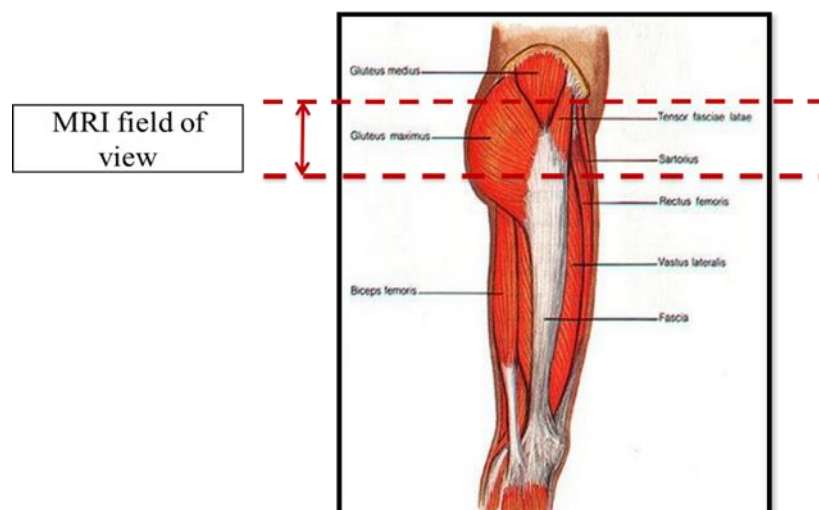


Figure 3-3: Approximate MRI field of view used for identifying hip muscles to be measured.

Radiological assessment

Anteroposterior radiographs of the hip were assessed by two trained readers using the OARSI (Osteoarthritis Research Society international) grading system. The radiographic features of JSN and osteophytes of the right hip were graded on a 4-point scale, ranging from 0 to 3 where 0=no disease and 3=most severe disease by using an Altman's atlas. The intra-observer reliability for x-rays was carried out in 40 subjects and the ICC scores ranged from 0.60-0.87. A non-zero score of either JSN or osteophytes was regarded as evidence of hip ROA. Thus, after combining JSN and osteophytes score, the presence of hip ROA was defined as a total score of 1 or greater.

Measurement of hip shape using dual-energy X-ray absorptiometry (DXA) images

At Phase 1, DXA images were taken of the left hip using a Hologic Delphi scanner. These images were extracted from the hologic data files (p files) using custom-made Matlab software (Math Works Inc, Natick, United States) and saved as 8bit BMP files as described in Figure 3-4. Once the images were converted they were uploaded in imaging software's customized for assessing bone shape.

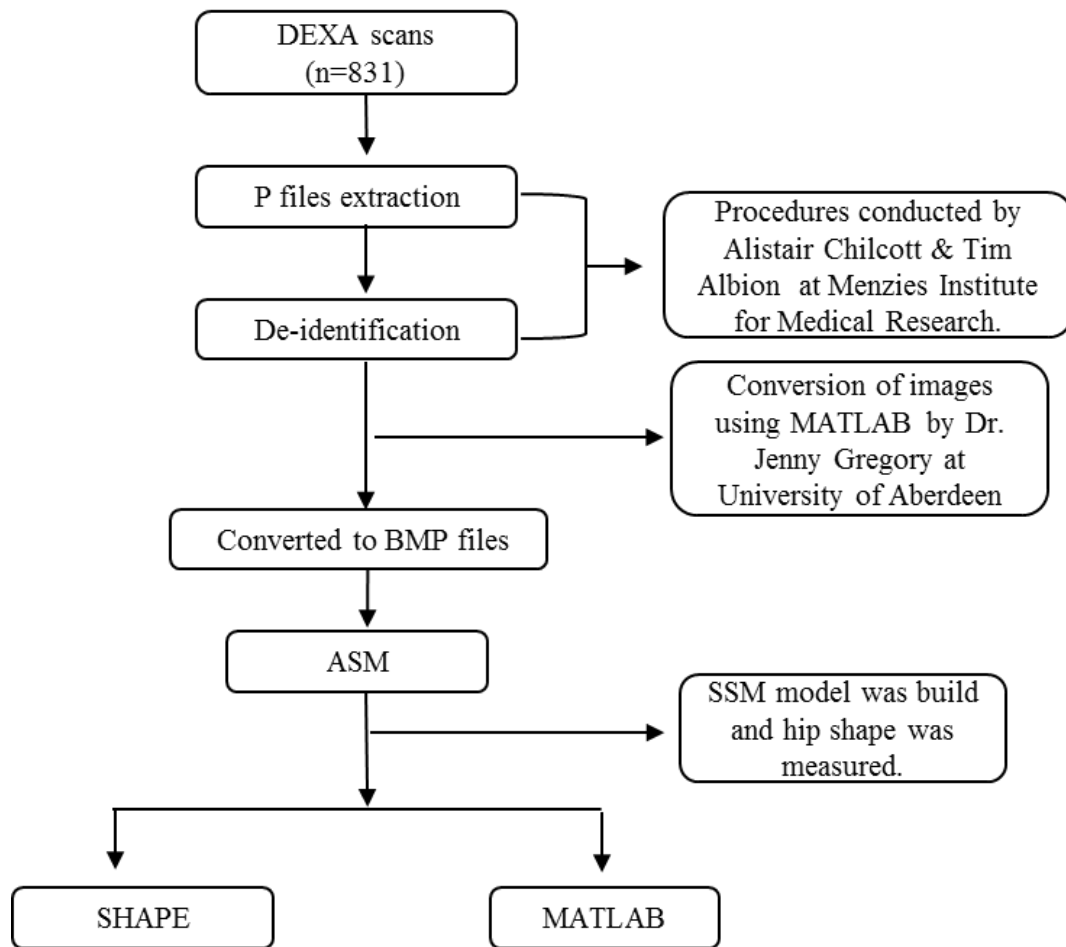


Figure 3-4: Flow chart describing processing of DEXA images for measuring hip shape.

Statistical shape modelling (SSM)

To quantify the morphology of the proximal femoral head, two types of imaging software were used. These were the ASM (Active Shape Modeling) toolkit (Manchester University, Manchester UK)^{174, 176} and SHAPE (University of Aberdeen, UK) software. The processed DXA images were transferred to a workstation and ASM was used to develop an 85-point model (Figure 3-5a). This model was designed not only to evaluate proximal femoral head shape but also the shape of the acetabulum and any osteophytes. The SSM template is a set of landmark points that define the shape to be identified. For comparison between several images, each point is placed at the same feature of the outline of the bone. Two types of points are used. The key points are placed at well-identified anatomical landmarks such as

beginning of greater trochanter, the highest point of the greater trochanter, higher and lower points of lesser trochanter; while the remaining points are evenly placed between the key points.

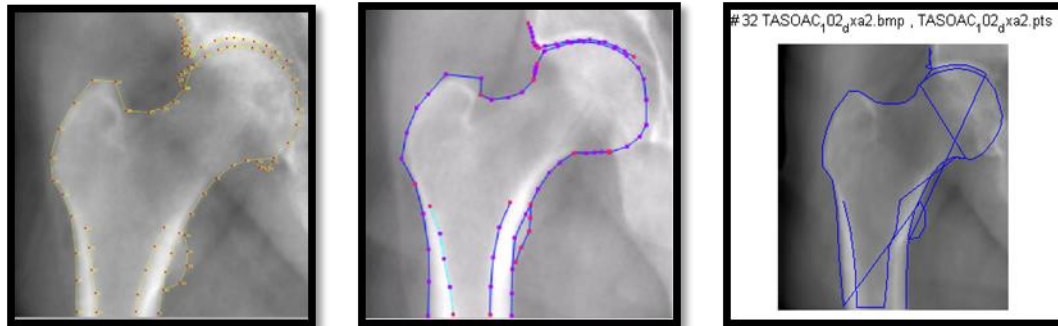


Figure 3-5: Examples of SSM of hip

- a) Illustration of 85-point shape model in ASM tool kit software b) Demonstrates the hip shape model in SHAPE software. c) Rechecking of data image generated by Matlab.

Once the measurements were compiled in (X, Y) coordinates using the ASM tool kit, the information was transferred onto SHAPE software in the form of a '*point file*'. The point file included the coordinates of each of the 85 points of the SSM model for each subject. The data were aligned into a common coordinate frame using Procrustes Analysis which translates, rotates and scales each shape so that it minimizes the sum of squared distances from the mean of the set.¹⁷⁶ The 85-point model was then compared with the DXA images to check the alignment of the points against the anatomical features, with adjustments made if necessary (Figure 3-5 b & c). The distribution of the data for all subjects was examined as a two-dimensional point cloud, allowing further checking for discrepant values (Figure 3-6). The SHAPE software was then used to extract the principal components of the data (each is referred to as a mode of shape). The first six principal components explained 68% of the variation of the data as shown in the scree plot in Figure 3-7. These shape modes have been extensively explained in chapter 9.

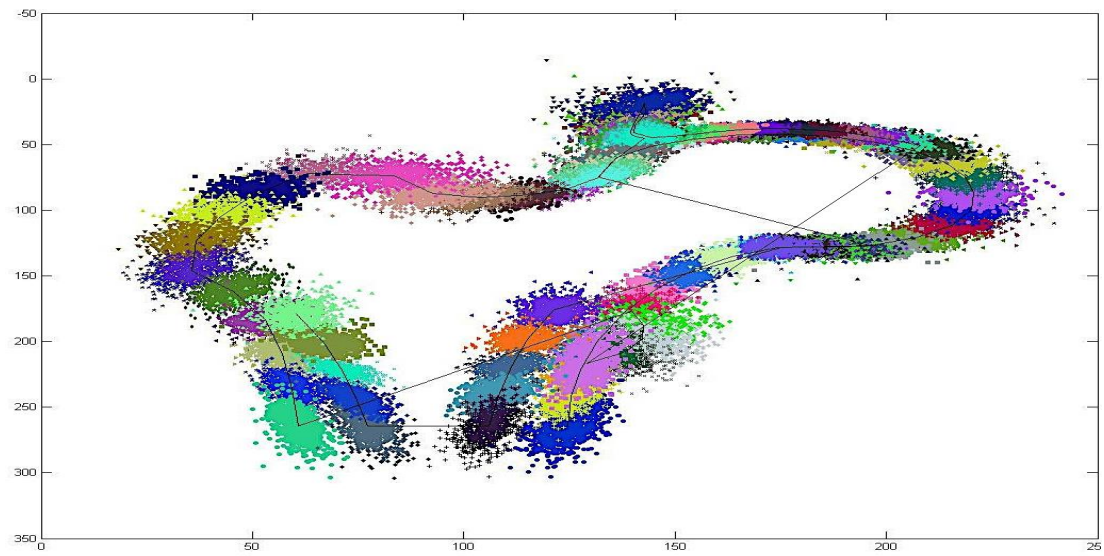


Figure 3-6: Two-dimensional point cloud of the hip shape data.

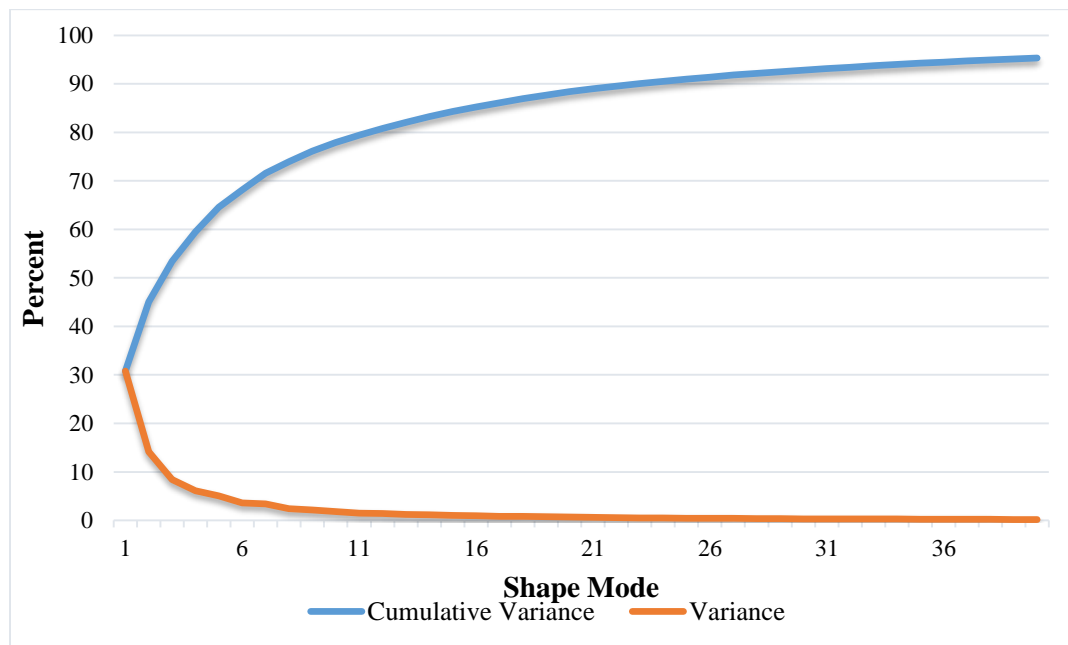


Figure 3-7: Scree plot representing variance and cumulative variance for 40 shape modes

Outcome factors, study factors, and covariates This research aims to gain further understanding of the pathophysiology of hip OA and to attain this goal it was critical to investigate the associations between clinical, radiological and MRI-related features pertaining to early hip osteoarthritic changes. Hence, each chapter of this thesis focuses on one structural change, describes its correlates and attempts to describe its relevance in early hip OA. Table 3-1 presents a summary of the outcomes, study factors and covariates involved in the analyses of each chapter that is included in this thesis.

Table 3-1: Summary of the outcome factors, study factors and covariates

Chapter	Outcome factors	Study factors	Covariates
4	Hip and knee pain*	Hip BMLs and high cartilage signal	Age, sex BMI
5	Total hip, femoral neck and spine BMD	Hip BMLs	Age, sex, BMI and spine BMD
6	Hip pain*, hip BMLs, high cartilage signal, hip ROA* and hip effusion-synovitis	Hip cartilage defects	Age, sex, BMI and hip BMLs.
7	Hip pain*, hip BMLs, high cartilage signal, hip ROA* and hip cartilage defects	Hip effusion-synovitis	Age, sex, BMI, hip BMLs and hip cartilage defects
8	Total hip, femoral neck and spine BMD	Muscle CSA Muscle strength	Age, sex, BMI and spine BMD.
9	Hip pain*, muscle strength, hip cartilage volume*, hip BMLs, hip cartilage defects, hip effusion-synovitis, hip ROA* and THR*	Hip shape	Age, sex, BMI, hip BMD.

* The measurement protocol used is described in the “Material and Methods” section of the relevant chapter.

BMLs: Bone marrow lesions, BMI: Body mass index, BMD: Bone mineral density, ROA: radiographic osteoarthritis, CSA: Cross-sectional area.

Sample size and the role of candidate in the TASOAC study

Data for the TASOAC study at Phase 1 (baseline), Phase 2 (first follow-up) and Phase 3 (second follow up) was already collected before the commencement of the candidate's PhD. Thus the number of participants included in each study reported in this thesis was limited to the numbers recruited at each phase of the TASOAC study, and for those whom measurements of the relevant outcome and study factors were available. All those with complete data on relevant outcomes and study factors were included in analyses of each study. The reasons for exclusion of other subjects have been exclusively described in each chapter. In consequence, formal sample size calculations were not undertaken as a part of the design of the studies reported in this thesis.

The candidate was involved in TASOAC data acquisition and collection, data management, data analyses and interpretation of results. The candidate was responsible for drafting and revising each manuscript. The candidate assisted in data collection at phase 4. Data acquisition for this study was conducted by a number of TASOAC staff and volunteers, including Prof Graeme Jones, Prof Chang-hai Ding, Dr. Dawn Aitken, Catrina Boon, Dale Pitt, Bronwyn Archer, Pam McDonald, Dr. Stella Foley, Tim Albion, Alistair Chilcott and Dr. David Scott. Many colleagues had begun using TASOAC data before the candidate commenced her Ph.D. The candidate gratefully acknowledges Dr. Guangju Zhai for measuring hip cartilage volume, and Dr. Dawn Aitken for cleaning and managing the datasets of measurements by DXA, pedometer counts, THR and muscle strength.

Ethical considerations

All procedures in the TASOAC study were approved by the Southern Tasmanian Health and Medical Human Research Ethics committee (Ethics Approval number: H6488). Written informed consent was obtained from all the participants prior to enrolment in the study.

Statistical analyses

T-test and chi-squared tests were used to compare differences in means and proportions as required. A p-value of <0.05 (two-tailed) was considered statistically significant. In several chapters, data on subjects at Phase 2 and Phase 3 were combined in analyses, and the correlation between repeated measurements on individuals was taken into account by adjusting standard errors using the sandwich (robust) estimator of variance. This sandwich estimator was developed by Huber¹⁸⁷ and White.¹⁸⁸ This estimator produces consistent standard errors from clustered data provided that the clusters are drawn as a simple random sample from its population.¹⁸⁹ The clusters in our analysis are repeated observations on the same person and that person was selected randomly from the population of southern Tasmania. Under this sampling design, the repeated observations within the clusters may not be treated as independent but the clusters are independent. The Huber-White method is generalized to this setting by substituting for the meat of the sandwich, a matrix formed from the outer product of the cluster-level score, where within each cluster the cluster-level score is obtained by summing the observations. *William et.al*¹⁹⁰ provides a general proof that this modified sandwich estimator is unbiased for cluster-correlated data regardless of the setting. This method has been described briefly in each study. Besides clustering, several other methods were applied to investigate the associations between outcomes and exposures and these have been described in detail in each chapter. All statistical analyses were performed on Intercooled Stata version 12 (Stata Corp, college station, TX, USA)

Preface

The aim of this thesis is to study the hip as a whole joint and to attempt to provide probable mechanisms relevant to the progression of hip OA. From here on, each chapter of this thesis addresses one research question which then contributes towards the overall aim of the thesis.

All the chapters of this thesis are based on TASSOAC cohort. This is a prospective population-based study which includes older adults between the ages of 65-80 years with mostly mild clinical or radiographic evidence of hip OA. Thus, in this thesis, we have referred to this cohort as '*preclinical hip OA*' or '*early hip OA*'.

Chapters 4-7, examine the associations of structural changes at the hip. These structural changes include hip BMLs, change in high cartilage signal, hip cartilage defects, and hip effusion-synovitis. Thus, each chapter focuses on only *one* structural change (except for BMLs) and reports its associations with various outcomes relevant for hip osteoarthritis.

Chapter 8 describe the association of hip muscles with muscle strength and bone mineral density and Chapter 9 aims to describe the associations of hip shape (morphology) over the period of 10-years

Chapter 4 : A population-based study of the association between hip bone marrow lesions (BMLs), high cartilage signal and hip and knee pain.



Published in the Journal of Clinical Rheumatology
2013, 33:369-376

Harbeer Ahedi, Dawn Aitken, Leigh Blizzard, Flavia Cicuttini and Graeme Jones
(Original article included as Appendix V)

Introduction

Osteoarthritis (OA) is a disease of the whole-organ characterized by gradual loss of articular cartilage. The prevalence of hip OA is lower than knee OA but is still a major cause of disability in the elderly.² Pain is one of the most common and important clinical symptoms in OA and has multiple causative factors.² Bone marrow lesions (BMLs) are now recognized as one of the key features in knee OA where they are associated with pain, cartilage loss^{107, 191} bone density^{63, 192} and joint replacement.^{107, 113} Studies demonstrate that participants with BMLs are at greater risk of worsening knee pain and size or grade of BMLs is correlated with intensity of knee pain.^{106, 107, 193} Longitudinal studies show that an increase in BML size is associated with an increase in knee pain^{106, 107, 110} while resolving BMLs were associated with a decrease in pain.^{107, 109} Recent data also suggests hand BMLs are independently associated with joint tenderness.¹⁹⁴ Evidence to date suggests that the association between BMLs and pain is local but it's unknown if the presence of BMLs at one joint is independently linked with painful adjoining joints.

To the best of our knowledge, there are very few studies on hip BMLs in relation to hip OA. In a retrospective MRI-based study involving 12 participants with advanced hip OA, *Boutry et.al* reported presence of hip BMLs in all the participants. Of these, all had femoral BMLs and 10/12 had acetabular BMLs. Histopathologically, the femoral head revealed severe degenerative changes, subchondral defects and articular trabecular fractures with fatty bone marrow.¹⁰² In a recent study, *Taljanovic et.al* evaluated the cross-sectional relationship between bone marrow edema size, clinical and radiological findings in hip OA in 16 participants. Despite the small sample size, focal bone marrow edema was found to correlate with hip pain ($r=0.51$, $p<0.05$). Further, in the same study subjects with hip BMLs had greater radiographic scores.¹⁰¹ Additionally, *Roemer et.al* used a semi-quantitative method to assessed hip BMLs and found no association between hip pain and hip BMLs although subjects with large hip BMLs tended to have higher odds of hip pain.⁹³ Nevertheless, no longitudinal studies have described the association between hip BMLs and hip pain.

Referred pain is common in OA and its occurrence may be due to neurological or biomechanical factors.¹⁹⁵ Studies have reported about 50% of subjects with hip pain also

report knee pain.¹⁹⁶ Khan *et.al* demonstrated that 27% of subjects awaiting total hip replacement (TKR) reported knee pain and it escalated (57%) in subjects requiring revised TKR.¹⁹⁵ Lastly, we have demonstrated an association between hip joint space narrowing (JSN) and knee pain.¹⁹⁷ Thus, it is possible that BMLs in the hip may also associate with knee pain but this concept has not been explored as yet.

Besides pain, BMLs of the knee are also associated with cartilage defects and volume.^{114, 198, 199} However, the assessment of cartilage volume and defects at the hip is challenging due to the complex structure of the hip joint. Although, these have been utilized in some studies^{93, 197}, additional techniques are required for assessing hip cartilage in a larger cohort. High cartilage signal is described as change in signal intensity of the articular cartilage due to increased water content in cartilage, which appears as a bright band in the cartilage on T2 MRI images.^{122, 124, 128} Studies suggest that before formation of cartilage defects or cartilage loss, vascularization and calcification of cartilage leads to changes in cartilage signal intensity.^{122, 128, 200} Totterman S.M *et.al* developed a quantitative method to analyze bone and cartilage of the knee, to test the longitudinal association between change in cartilage signal, progression of knee OA and pain. The authors found that signal intensity of central femur regions was correlated with progression of knee OA and change in signal intensity in medial and lateral femoral compartments was associated with change in knee pain.^{128, 200} To date, there are no studies at the hip.

Hence, the aim of this population-based study was to describe the cross-sectional and longitudinal relationship between hip BMLs, high cartilage signal and hip and knee pain.

Materials and methods

Subjects

This study was conducted as a part of the Tasmanian Older Adult Cohort (TASOAC) study, a prospective, population-based study initiated in 2002 aimed at identifying the environmental, genetic and biochemical factors associated with the development and progression of OA at multiple sites (hand, knee, hip and spine). Subjects between the ages of 50 to 80 years were selected from the electoral roll of Southern Tasmania (population 229,000) using a sex-stratified simple random sampling technique. The overall response rate was 57%. As

TASOAC was designed to examine community-dwelling older adults, institutionalized older adults were excluded. Participants were also excluded if they reported contraindication for MRI. Of all initially eligible participants, 1,100 enrolled in the study, and 1,099 attended a baseline (Phase 1) clinic between March 2002 and September 2004. Follow-up data (Phase 2) was collected for 875 participants at a clinic approximately three years later, and then again for 769 participants (Phase 3) at a clinic approximately five years later.

During the TASOAC study, a hip protocol was added during the latter part of phase 2. In the current study a sample of 245 consecutive participants which had a STIR (Short T1 Inversion Recovery) MRI sequence at phase 2 and/or phase 3 were included. Of these 245 participants, 30 participants were lost to follow-up at phase 3 and 17 participants did not have a STIR sequence at phase 2 hence the total number of participants who had a hip STIR MRI scan at both phases was 198 (figure 4-1). This study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and written informed consent was obtained from all participants.

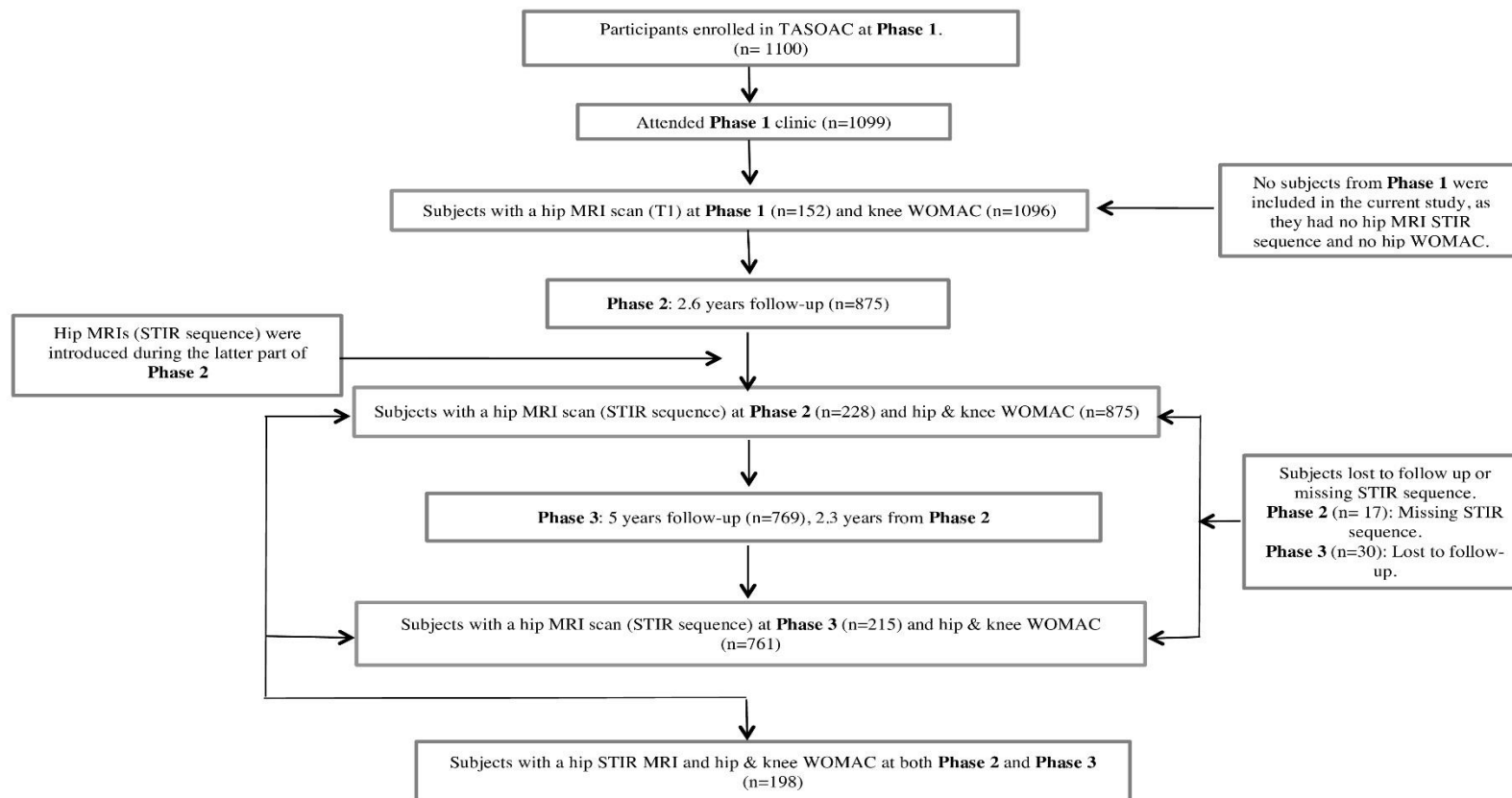


Figure 4-1: Sample population inclusion flow chart

Clinical measurements

Demographic characteristics, medical history and lifestyle factors were assessed by self-administered questionnaires. Height was measured to the nearest 0.1 cm using a stadiometer (with shoes, socks and bulky clothes removed). Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothes removed) using a single pair of electronic scales (Seca Delta model 707; Hamburg, Germany). Body mass index (BMI) was calculated.

Magnetic Resonance Imaging

An MRI scan of the right hip was performed. The hip was imaged in the sagittal plane using a 1.5 Telsa G.E signal whole-body magnetic resonance unit with a phased-array flex coil. The following image sequence was used: STIR-weighted fat saturation two dimensional fast spin echo sequence; repetition time 4340 msec, echo time 28.4 msec; field of view 20 cm; 15 partitions and 512 x 512-pixel matrix. Sagittal images were obtained at slice thickness of 3.5 mm with an interslice gap of 1.5mm.

Measurement of hip BMLs

For quantitative assessment of subchondral hip BMLs on STIR-weighted MR images, Osiris X software (University of Geneva, Geneva, Switzerland) was used. BMLs were identified as areas of increased signal intensity adjacent to the subchondral bone on the femoral head and/or the acetabulum. The slices were divided into femoral and acetabular regions. One trained observer assessed hip BML size by measuring the maximum area of the lesion at both baseline and follow-up. The observer manually selected the MR slice with the largest BML and then determined the BML size by manually drawing contours around the outer edges of the lesion (Figure 4-2). Intra-observer repeatability was assessed in 25 subjects (at both time points) with a two-week gap between the measures. The intra-class correlation coefficient (ICC) for hip BMLs was 0.98, similar to the reproducibility of our knee quantitative BML measure¹⁰⁷.

High Cartilage Signal

The presence of high cartilage signal at the hip joint was defined as high signal intensity band within the cartilage either adjacent to the hip BML or at any location on the STIR MR slice if there was no BML. High cartilage signal was graded as 0 for absent and 1 for present (Figure 4-2) by the same observer along with hip BMLs. The reproducibility was assessed in 25 subjects (at both time points) with a two-week interval between the readings. The intra-rater agreement (kappa) for high cartilage signal was excellent at 0.88.

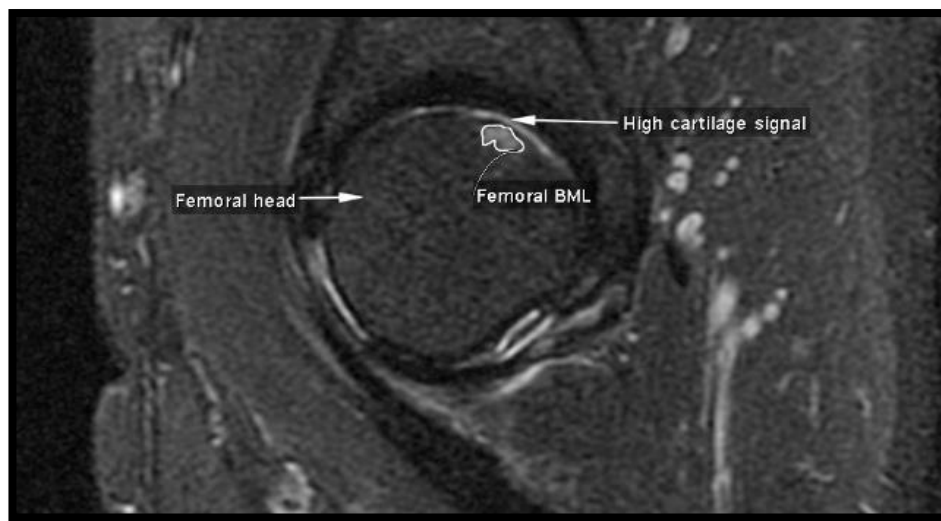


Figure 4-2: Measurement of femoral BML size with an adjacent high cartilage signal

WOMAC scores

Hip and knee pain for all the subjects who had a hip MRI was determined using a hip specific and knee specific Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index pain score. WOMAC uses a 10-point scale from 0 (indicating no pain) to 9 (indicating severe pain). For the purpose of this study pain in the hips (5 items) and knees (5 items) was assessed separately using the following questions: Referring to your hips only how much pain did you experience when walking on flat surface, going up and down the stairs, at night while in bed, sitting or lying and standing upright.⁸⁹ These 5 items were summed to create a total hip and total knee pain score each with a possible range from 0 – 45.

Statistical analyses

Descriptive data were summarized as means and standard deviations with right skewed data transformed by taking logarithms. Differences in demographical characteristics were calculated using unpaired t-tests and chi-square tests. Due the lack of overall associations between BMLs and pain, we performed an exploratory data driven analysis (post-hoc analysis). This resulted in a femoral BML area less than 0.45cm^2 being categorized as small and one greater or equal to 0.45cm^2 being categorized as large. Similarly, acetabular BMLs of size less than 1.5cm^2 were categorized as small while those greater than or equal to 1.5cm^2 were categorized as large. Small femoral and acetabular BMLs were combined together and labeled as any small BMLs. Large acetabular and femoral BMLs were combined together and labeled as any large BMLs. No subject had a large femoral and small acetabular or a small femoral and a large acetabular BML. For determining the relationship between presence of pain and presence of hip BMLs, WOMAC score was modified into a binary variable, where subjects with no pain were graded as 0 and subjects with pain >0 were graded as 1.

In the cross-sectional analysis, logistic regression was used to compare the odds of no pain (pain score=0) and the odds of pain (pain score >0), and linear regression was used to model the pain scores of those with pain in analysis restricted to those with a non-zero pain score. Further, odds of presence or absence of high cartilage signal were estimated using logistic regression. Data on subjects at phase 2 and phase 3 were combined in analyses, and the correlation between repeated measurements on individuals was taken into account by adjusting standard errors using the sandwich (robust) estimator of variance.

For longitudinal analysis, linear regression models were used to estimate the association between change in hip and knee pain scores and presence or absence of BMLs. For the purpose of this analyses, hip BMLs present at baseline and not at follow-up were categorized as resolved BMLs, and hip BMLs present at follow-up but not at baseline were categorized as incident BMLs. Additionally, these methods were also used to estimate the association of change in pain and change in hip BML size from baseline to follow-up for subjects with a BML at either time point. All models were adjusted for age, sex and body mass index. Further, models for hip pain were adjusted for knee pain and models for knee pain were

adjusted for hip pain. All statistical tests were two sided and p values < 0.05 were considered significant. All statistical analysis was conducted using Intercooled Stata 12 for Mac (Stata Corp, College station, TX, USA).

Results

Characteristics of the population

Table 4-1 outlines the demographic characteristics of the sample population. The data is presented for those with and without any BML. A total of 28% (n=55/198) had one or more BMLs and 8% (n=15/198) had large BMLs present at the femoral and/or acetabular site. Age, height, weight and BMI of participants with or without hip BMLs were similar, but males were over represented in subjects with BMLs. On average, femoral BML size (0.15 cm²) was smaller than acetabular BML size (0.74 cm²). The percentage with high cartilage signal was higher in subjects with hip BMLs when compared with those without hip BMLs. Proportions with knee and hip pain tended to be lower in the hip BML group but there was no statistically significant difference. Additionally, knee pain was more common but generally less severe than hip pain.

Table 4-1: Characteristics of the population

Characteristics	Any hip BML		P values
	Hip BML absent (n=143)	present (n=55)	
Mean age (yrs.)	64.3 (7.07)	64.5 (6.40)	0.90
Male sex	54%	62%	0.33
Mean height (cms)	167 (9.15)	168 (9.00)	0.31
Mean weight (kgs)	77.8 (14.3)	77.1 (14.8)	0.65
Mean BMI (kg/cm ²)	27.8 (4.40)	27.2 (4.61)	0.35
Mean femoral CSA (cm ²)	-	0.15 (0.41)	-
Mean acetabular CSA (cm ²)	-	0.74 (0.55)	-
High cartilage signal	51%	87%	<0.001
Presence of knee pain	71%	67%	0.45
Severity knee pain score*	2.47 (0.39)	2.38 (0.35)	0.87
Presence of hip pain	33%	25%	0.27
Severity hip pain score*	3.89 (0.67)	3.10 (0.94)	0.33

Data presented in means (SD)

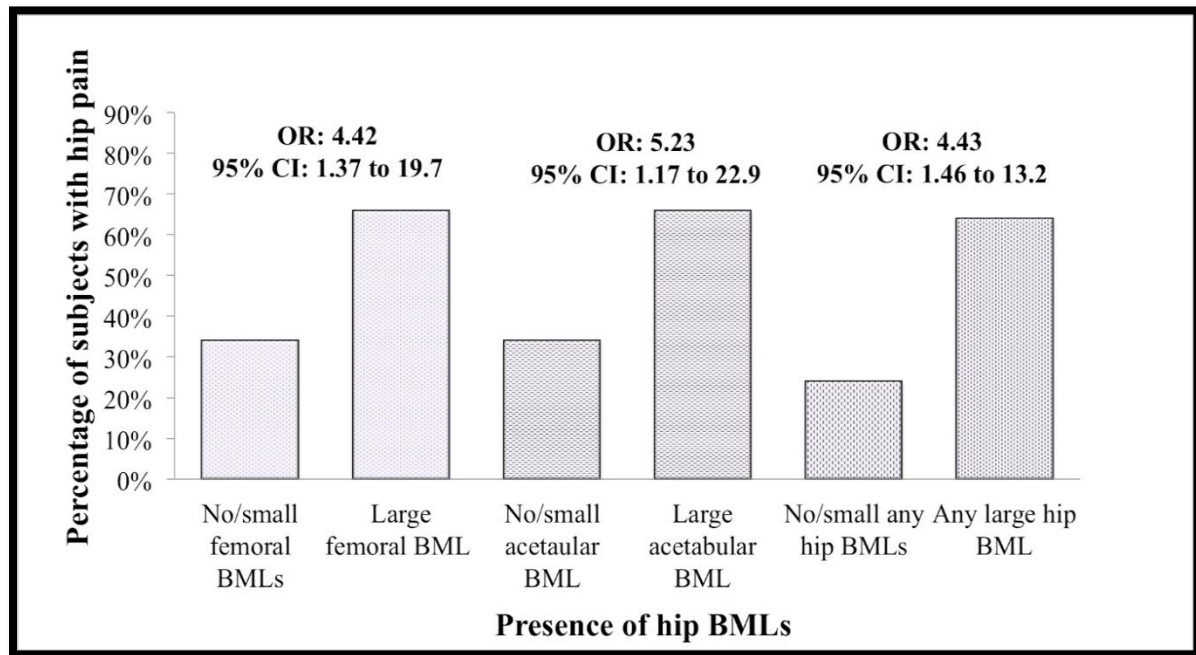
Bold face indicates statistically significant results ($p < 0.05$)

Pain score calculated by using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

* Pain score presented after log transformation.

Hip BMLs and hip pain

Figure 4-3 shows the cross-sectional association between presence of no/small and large hip BMLs with presence of hip pain. Only presence of large hip BMLs, irrespective of BML site, were associated with higher odds of hip pain.



Dependent variable: hip pain. Independent variable: hip BMLs. Y-axis: Percentage of subjects with hip pain. X-axis: Subjects with no/small and large hip BMLs. Odds ratios and confidence intervals, adjusted for age, sex and body mass index and clustering of observations of subjects at phase 2 and phase 3 was taken into account. Further, models were adjusted for presence of knee pain. Boldface indicates statistically significant results.

Figure 4-3: Cross-sectional relationship between presence of BMLs and presence of hip pain.

Hip pain severity and large hip BMLs

Cross-sectionally severity of hip pain (WOMAC>0) was not associated with presence of large hip BML (Table 4-2). However, severity of hip pain was associated with per cm² increase in size of acetabular BML (β : 4.18; 95% CI: 1.54, 6.88) but not with increase in size of femoral or any BML. Longitudinally, resolving acetabular BMLs had no association with hip pain while incident femoral and acetabular BMLs were strongly associated with an increase in hip pain (Table 4-3). Lastly, change in any BML size was significantly associated with change in hip pain (Table 4-4).

Hip BMLs and knee pain

Cross-sectionally, presence of knee pain or severity of knee pain (table 4-2) was not associated with hip BMLs. Longitudinally, despite the small number with change in BMLs, an association between resolving femoral BMLs and knee pain was noted (table 4-3). Lastly, change in knee pain from baseline to follow up showed no association with change in hip BML size at any site (table 4-4).

Hip BMLs and high cartilage signal

The odds of presence of high cartilage signal intensity were much higher in subjects with any hip BML [OR: 6.45, 95% CI: 3.37, 12.6], especially in those with acetabular BMLs [OR: 8.41, 95% CI: 3.68, 19.4].

Table 4-2: Cross-sectional relationship between severity of pain (WOMAC scores) and presence of large BMLs

Study factor	Hip pain			Knee pain		
	N*	Mean(SD)	Difference	N*	Mean(SD)	Difference
			Mean(95% CI) [†]			Mean(95% CI) [†]
Femoral BML						
No/small BMLs	142	6.03 (6.93)]	-1.54 (-3.98, +0.93)	304	3.58 (3.60)]	-0.34 (-1.24, +0.50)
Large BMLs (≥0.45 cm²)	6	4.33 (3.20)]		7	3.61 (1.13)]	
Acetabular BML						
No/small BMLs	144	5.83 (6.81)]	+3.35 (-2.46, +9.05)	307	3.55 (3.65)]	-0.89 (-3.92, +2.39)
Large BMLs (≥1.5 cm²)	4	10.50 (4.04)]		4	5.50 (1.73)]	
Any BML[‡]						
No/small BMLs	139	5.90 (6.99)]	+0.43 (-3.16, +4.03)	301	3.55 (3.61)]	-0.43 (-1.97, +1.04)
Large BMLs	9	6.77 (4.93)]		10	4.30 (1.70)]	

Dependent variable: Hip and knee pain score (WOMAC). Independent variable: presence of hip BMLs.

*Numbers shown are from measurements of 198 subjects at phase 2 & phase 3 and include repeated observation on the same subjects. Further, these analysis only includes subjects with a WOMAC score > 0.

[†] Data adjusted for age, sex and body mass index and with clustering of observations on individuals taken into account. Further hip pain models were adjusted for presence of knee pain and knee pain models for presence of hip pain.

[‡] Any large BMLs: category including the combination of femoral BMLs ≥ 0.45 & acetabular BML ≥ 1.5 .

Boldface indicates statistically significant results (P < 0.05)

Table 4-3: Longitudinal association between change in prevalence of large BMLs and change in pain

Study factor	n	Hip pain		Knee pain	
		Means (SD)	Adjusted Mean difference (95% CI) [†]	Means (SD)	Adjusted Mean difference (95% CI) [†]
Femoral BML (>0.45 cm ²)					
Absent	188	0.09 (4.94)		1.04 (3.32)	
Resolving BML	2	−3.00 (2.82)	−2.24 (-4.76, +0.41)	−2.00 (2.83)	− 3.18 (-5.99, -0.50)
Incident BML	4	0.75 (0.50)	+1.18 (+0.23, +1.94)	0.25 (2.43)	−0.71 (-2.53, +1.12)
Acetabular BML (>1.5 cm ²)					
Absent	192	0.06 (4.90)		1.00 (3.34)	
Resolving BML	2	0.00 (N.A)	+0.42 (-0.64, +1.45)	1.00 (N.A)	−0.37 (-1.17, +0.43)
Incident BML	1	4.00 (N.A)	+5.90 (+3.78, +8.15)	0.00 (N.A)	−0.81 (-2.34, +0.72)
Any BML [‡]					
Absent	185	0.07 (4.97)		1.05 (3.32)	
Resolving BML	4	−1.50 (2.40)	−0.95 (-2.85, +1.04)	-0.50 (2.40)	−1.81 (-3.82, +0.21)
Incident BML	5	1.40 (1.52)	+2.08 (+0.22, +3.94)	0.20 (2.05)	−0.75 (-2.34, +0.82)

Dependent variable: change in hip and knee pain. Independent variable: change in prevalence hip BMLs.

*n indicates number of subjects with pain (n)/total number of subjects in each category.

†Data adjusted for age, sex and body mass index. Further hip pain models were adjusted for change in knee pain and knee pain models for change in hip pain.

‡Any BMLs: category including the combination of femoral BMLs ≥ 0.45 & acetabular BML ≥ 1.5 .

Analysis excludes one subject with BML at both time points.

Boldface indicates significant results

Table 4-4: Relationship between change in hip BML size and change in pain

Study factor	Change in hip pain	Change in knee pain
	βeta (95% CI) †	βeta (95% CI) †
Femoral BML size (cm ²)	+0.96 (-0.55, +1.96)	+1.02 (-0.76, +2.80)
Acetabular BML size (cm ²)	+0.80 (-0.42, +2.90)	-1.90 (-2.00, +0.30)
Any BML size‡ (cm ²)	+0.85 (-0.00, +1.71)	-0.42 (-1.41, +0.61)

Dependent variable: change in hip and knee pain. Independent variable: change in hip BML size.

βeta coefficient indicates the values of change in pain score per 1 unit change in BML size (cm²)

†Data adjusted for age, sex and body mass index. Further, hip pain models were adjusted for change in knee pain and knee pain models for change in hip pain.

‡ Any BMLs: category including the combination of femoral BMLs & acetabular BMLs.

Boldface indicates significant results.

Discussion

This is the first large population-based study describing the cross-sectional and longitudinal relationships of hip BMLs with pain at either the hip or knee joint. A total of 28% had a BML of which 8 % were large. Of these, only large BMLs were associated with pain, most notably at the hip. Incident but not resolving BMLs were associated with changes in hip pain and only resolving femoral BMLs were associated with decrease in knee pain. Lastly, there was also a strong association of hip BMLs with high cartilage signal.

The nature of pain in OA is controversial. Studies show, with some exceptions, that knee BMLs, especially large ones, are associated with knee pain.^{193, 197} In our study, presence of large hip BMLs was associated with overall fourfold higher odds of hip pain. Further, acetabular BML size was associated with more severe hip pain. These findings are supported by *Taljanovic's* study in which focal hip BMLs were significantly correlated with hip pain.¹⁰¹ Further, *Roemer et.al* also reported that subjects with grade 3 hip BMLs had higher odds of having hip pain [OR: 6.10, 95% CI 0.75, 49.6] but this association didn't reach statistical significance.⁹³

In the second part of our study, we analyzed the longitudinal association between change in pain and change in hip BML presence and BML size over approximately 2.3 years. Despite the small numbers of changing BMLs there were a number of significant results. Incident large hip BMLs (femoral or acetabular) were independently associated with worsening hip pain while any large resolving femoral BML was also independently associated with reduced knee pain. Furthermore, increase in BML size was associated with an increase in hip pain. These findings are similar to longitudinal data on knee BMLs,^{106, 107, 193} however the association between resolving femoral BMLs and knee pain is novel. We have reported an association between hip JSN and knee pain¹⁹⁷ and previous studies have described a strong link between hip and knee pain in hip OA.^{195, 196} Based on our findings, it can be speculated that besides JSN, hip BMLs might also be one of the causes of referred knee pain. However, this finding requires confirmation in studies conducted in subjects with severe hip OA and a higher prevalence of BMLs.

Previous studies based on assessing cartilage signal intensity suggest that high cartilage intensity on MRI can be used as a predictor to detect early degeneration of articular cartilage.^{122, 124, 127} In the present study, high cartilage signal was strongly associated with the presence of large BMLs (most notably acetabular) but not with pain, which contrasts with the

study conducted by *Totterman et.al* that reported change in cartilage signal was positively correlated with change in knee pain. These differences may be due to site variations (hip and knee) and/or the methodology as change in cartilage signal appears to be a marker for changes in cartilage composition¹²⁴. Hence, change in the cartilage signal is likely to reflect deleterious changes in articular cartilage at either site. The cross-sectional nature of this analysis does not allow causal inferences to be made. Additionally, these may well be interdependent as has been seen at the knee where, using longitudinal data, *Dore et.al* reported higher cartilage defect worsening in subjects with knee BMLs and vice versa¹¹⁴.

Limitations

This study has a few potential limitations. The analyses were carried out with a relatively small number of large hip BMLs, nevertheless most of our hip pain results were consistent and statistically significant. Further, these analyses are based on data driven cut points which should be considered hypothesis generating and require confirmation in other studies. WOMAC scores used in this study assessed hip and knee pain separately; however, did not differentiate between right/left sides. Hence, we were unable to conduct analysis that only included subjects with pain in the right hip or knee. Additionally, this study included some subjects who reported both hip and knee pain, thus we adjusted all models for pain (hip models for knee pain and vice versa) in order to examine the independent associations. The scoring of BMLs at the hip and the use of cross-sectional BML area is novel and reflects our experience with knee BMLs and has good performance characteristics suggesting measurement error is not substantially affecting our results.

Conclusions

In conclusion, the evidence is consistent for hip but not knee pain, and strongly suggests that large hip BMLs are associated with hip pain. Further, high cartilage signal is asymptomatic but strongly associated with hip BMLs. These findings suggest hip BMLs play an important role in hip OA.

Postscript

Hip BMLs are rare in older adults. This study determines that hip BMLs are one of the causes of hip pain and perhaps referred knee pain. Regardless of size, hip BMLs were strongly associated with early changes in the hip cartilage (high cartilage signal) revealing that subchondral BMLs have an impact on cartilage health. Along with pain, BMLs are also known to associate with changes in the bone density. Thus, the next chapter focuses on describing the relationship between BMLs and BMD.

Chapter 5 : The Association between Hip Bone Marrow Lesions and Bone Mineral Density: A Cross-sectional and Longitudinal Population-based Study.



Published in Osteoarthritis and Cartilage

2013 19:838-838

Harbeer Ahedi, Dawn Aitken, Leigh Blizzard, Flavia Cicuttini and Graeme Jones.

(Original article included as Appendix VI)

Introduction

Bone marrow lesions (BMLs) are a key features of osteoarthritis (OA) and are associated with pain¹⁰⁷, cartilage defects, cartilage volume loss¹¹⁴ and joint replacement.¹⁰⁷ Similarly, BMLs of the hip are associated with hip pain and hip joint space narrowing.¹⁰¹

Bone density is usually higher in subjects with OA²⁰¹ and its relationship with knee BMLs has been explored. *Lo et.al* documented an increased ratio of compartment specific local tibial BMD in association with knee BMLs.²⁰² We found a positive correlation between knee BMLs and subchondral bone density in a community based sample.²⁰³ Furthermore, *Hunter et.al*, demonstrated an increased bone volume fraction but a decrease in tissue mineral density in cores of bone area affected by knee BMLs in women awaiting knee replacement.⁶³ The increase in bone density may be due to ongoing remodeling of damaged trabeculae in areas where BMLs were located.²⁰²

Studies looking into the association between BMLs and bone density in joints other than the knee are limited.²⁰⁴ Similar changes in bone density are seen in subjects with hip OA,²⁰¹ however the association between hip BMLs and BMD is yet to be examined. Hence, the aims of this study were to describe the cross-sectional and longitudinal relationship between hip BMLs and total hip, femoral neck and spine BMD.

Materials and Methods

Subjects

The Tasmanian Older Adult Cohort (TASOAC) study is a population-based cohort and the study design has been extensively described in previous manuscripts.^{107, 114, 203} The hip protocol was added during the latter part of phase 2. In the current study a sample of 245 consecutive participants with a STIR (Short T1 Inversion Recovery) MRI sequence at phase 2 and/or phase 3 were included (figure 5-1). Of these 245 participants, 30 participants were lost to follow-up at phase 3 and 17 participants had missing STIR sequences at phase 2 hence the total number of participants who had a hip STIR MRI scan at both phases was 198. This study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and written informed consent was obtained

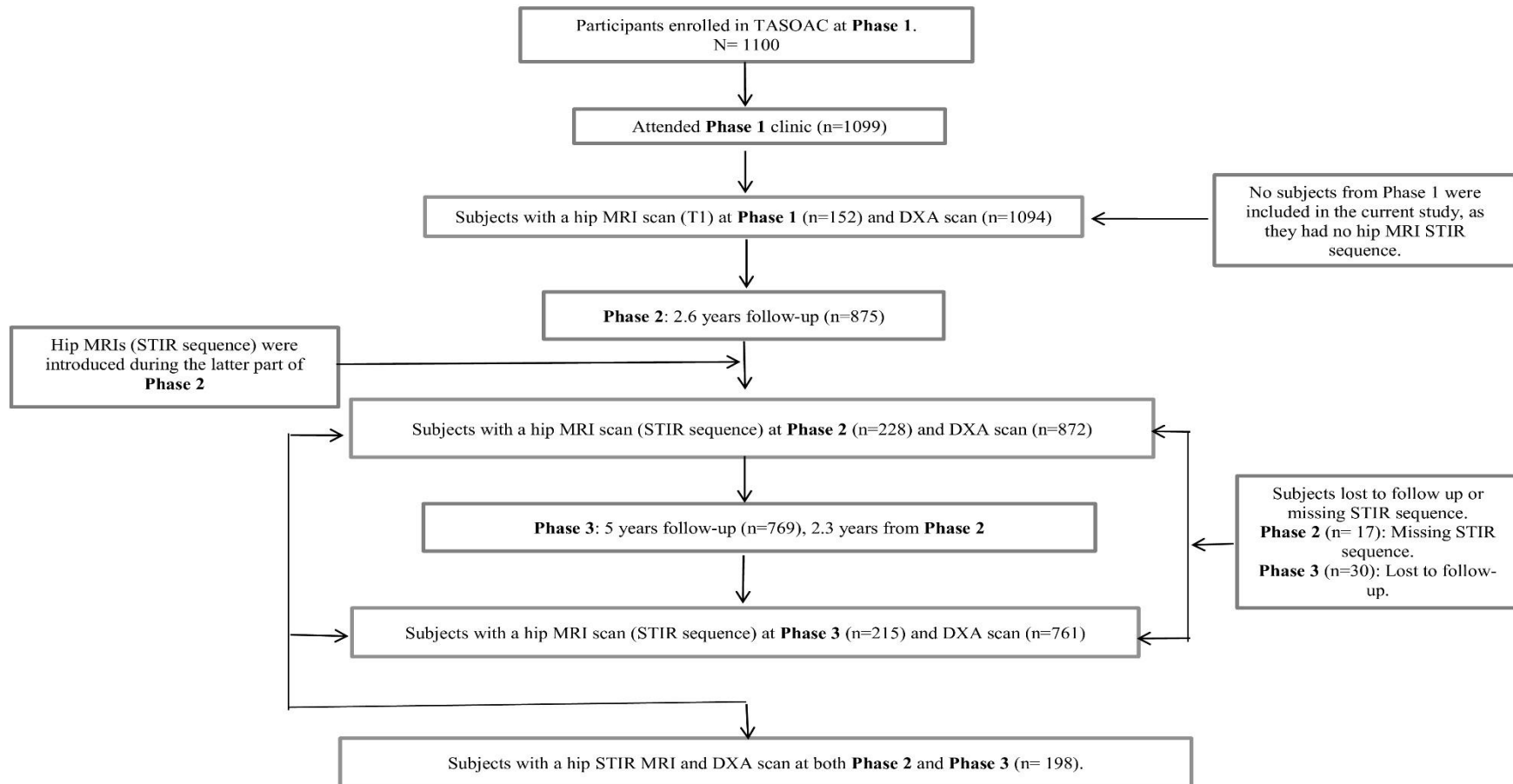


Figure 5-1: Sample population inclusion chart

Clinical and DXA measurements

Height, weight and BMI were measured using standard protocols. BMD of the hip, femoral neck and spine at both phase 2 and phase 3 was assessed by DXA using a Hologic Delphi scanner as previously described.²⁰³

Magnetic Resonance imaging

The right hip was imaged in the sagittal plane using a 1.5 Tesla G.E signal whole-body magnetic resonance unit with a phased-array flex coil. The following image sequence was used: STIR-weighted fat saturation two dimensional fast spin echo sequence; repetition time 4340 msec, echo time 28.4 msec; field of view 20 cm; 15 partitions and 512 x 512-pixel matrix. Sagittal images were obtained at slice thickness of 3.5 mm with an interslice gap of 1.5mm.

Measurement of hip BMLs

For quantitative assessment of subchondral hip BMLs OsiriX software (University of Geneva, Geneva, Switzerland) was used. Hip BMLs were identified as areas of increased signal intensity adjacent to the subchondral bone on the femoral head and/or the acetabulum. One trained observer manually selected the MR slice with the largest BML and then scored the maximum area (cm²) of all the identified lesions by manually drawing contours around their outer edges (figure 5-2). The BML with the highest score was used if more than one lesion was present at the same site. Intra-observer repeatability was assessed and the intra-class correlation coefficient (ICC) of the hip, femoral and acetabular BMLs was 0.98, 0.96 and 0.99 respectively (n=25), similar to the reproducibility of our knee quantitative BML measure¹⁰⁷.

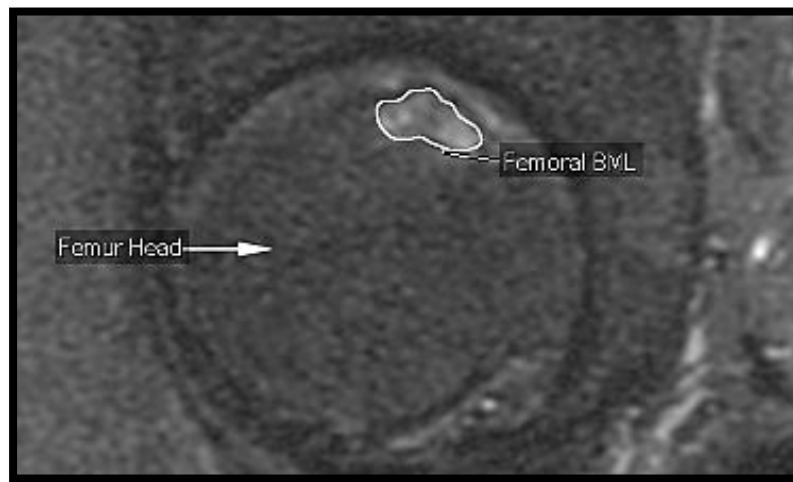


Figure 5-2: Measurement of femoral BML

Statistical analysis

Student's t-tests and chi-squared tests were applied to determine the differences in means and proportions. The fit of all models were tested and all assumptions were fulfilled. Cross-sectional and longitudinal analyses were based on linear regression. Cross-sectionally, the relationship between hip BML presence or absence and BMD of the hip, femoral neck and spine was estimated by determining the mean difference in BMD of subjects with and without hip BMLs. These analyses were adjusted for age, sex, BMI and presence or absence of radiological hip OA, as adding covariates for these factors to the models changed the estimated coefficient of the study factor (BMLs) by more than 10%. For all cross-sectional analyses, data on subjects at phase 2 and phase 3 was combined and the correlation between repeated measurements on individuals was taken into account by adjusting standard errors using the sandwich (robust) estimator of variance.^{[187](#), [188](#), [190](#)} Lastly, the relationship between change in BML size and change in BMD of the hip, femoral neck and spine from baseline to follow-up for subjects with a BML at either time point was analyzed. All models were adjusted for age, sex and body mass index. All statistical tests were two sided and p values < 0.05 were considered significant.

Results

Characteristics of the sample population

Of the 198 subjects, 28% (N=55) had a hip BML. Subjects with and without BMLs were similar in gender distribution (62% v 54% male), mean age 64yrs for both and mean (SD) BMI [27.2 (4.40) v 27.8 (4.61)]. BMD at the hip, spine and femoral neck was lower in subjects with any hip BML and the difference at the femoral neck [p=0.03] was statistically significant. Lastly, acetabular BMLs [mean (SD): 0.74 (0.55)] were larger in comparison to femoral BMLs [mean (SD): 0.15 (0.41)].

Cross-sectional relationship between hip BMLs and BMD

Table 5-1 shows the cross-sectional relationship between hip BML presence and BMD at the hip, femoral neck and spine. The presence of acetabular BMLs was associated with lower BMD at the hip and femoral neck. Further, these associations persisted after adjustment for radiographic hip OA. BML size was not significantly associated with BMD but subjects with femoral BMLs had 12% lower femoral neck BMD as the difference in BMD per unit increase in femoral BML was -0.12 (95% CI -0.24, +0.01).

Table 5-1 Cross-sectional relationship between presence of hip BMLs and bone density at the hip, femoral neck and spine

BML Category	Total hip BMD (g/cm ²)			Femoral neck BMD (g/cm ²)			Spine BMD (g/cm ²)		
	N*	Mean (SD)	Adjusted mean Difference (95% CI) [†]	N*	Mean (SD)	Adjusted mean Difference (95% CI) [†]	N*	Mean (SD)	Adjusted mean Difference (95% CI) [†]
Femoral BML									
No BML	412	0.97 (0.14)		412	0.77 (0.11)		414	1.02 (0.16)	
BML Present	15	0.99 (0.13)	+0.01 (−0.07, +0.10)	15	0.80 (0.11)	+0.02 (−0.06, +0.17)	15	1.03 (0.11)	<0.01 (−0.08, +0.08)
Acetabular BML									
No BML	361	0.98 (0.14)		361	0.79 (0.11)		363	1.03 (0.15)	
BML Present	66	0.93 (0.12)	−0.05 (−0.09, −0.01)	66	0.73 (0.08)	−0.06 (−0.09, −0.03)	66	1.00 (0.15)	−0.03 (−0.08, +0.01)

Dependent variable: BMD. Independent variable: Presence or absence of BMLs.

Data adjusted for age, sex, body mass index and radiological hip OA (ROA).

Boldface indicates statistically significant results (P<0.05)

N* Numbers shown are from measurements of 198 subjects at phase 2 & phase 3 and include repeated observation on the same subjects. Moreover, data for total hip and femoral neck BMD for one subject at phase 2 and 1 subject at phase 3 was missing.

Longitudinal association between hip BML and BMD

Table 5-2 presents the association between incident and resolving hip BMLs and change in BMD. Resolving femoral BMLs were associated with a decrease while incident femoral BMLs were associated with an increase in femoral neck BMD. Conversely, resolving acetabular BMLs were associated with an increase in hip and femoral neck BMD while incident acetabular BMLs were not associated with BMD at any site. Persistent hip BMLs were not associated with changes in bone density.

Table 5-2 Longitudinal relationship between change in prevalence of hip BMLs and change in bone density of hip, femoral neck and spine

BML Category	N*	Change in total hip BMD (g/cm ²)	Change in femoral neck BMD (g/cm ²)	Change in spine BMD (g/cm ²)
		Difference in mean (95% CI) [†]	Difference in mean (95% CI) [†]	Difference in mean (95% CI) [†]
Femoral BML				
No BMLs	175			
Resolved BML	2	−0.03 (−0.09, +0.03)	−0.04 (−0.09, −0.01)	−0.03 (−0.09, +0.03)
Incident BML	4	+0.02 (−0.00, +0.04)	+0.03 (+0.02, +0.04)	<0.01 (−0.02, +0.01)
Persistent BML	4	−0.01 (−0.04, +0.01)	<0.01 (−0.02, +0.03)	−0.03 (−0.06, −0.00)
Acetabular BML				
No BML	146			
Resolved BML	12	+0.02 (−0.00, +0.34)	+0.01 (+0.00, +0.03)	<0.01 (−0.02, +0.02)
Incident BML	10	<0.01 (−0.01, +0.23)	<0.01 (−0.01, +0.02)	<0.01 (−0.02, +0.01)
Persistent BML	19	<0.01 (−0.02, +0.01)	<0.01 (−0.02, +0.01)	−0.02 (−0.04, −0.00)

Dependent variable: change in BMD. Independent variable: change in prevalence of BMLs.

*Number of subjects in each category excluding participants with missing data at baseline or follow-up.

† Data adjusted for age, sex and body mass index.

Boldface indicates statistically significant results (P<0.05)

For these analyses, hip BMLs present at baseline and not at follow-up were categorized as resolved BMLs. Hip BMLs present at follow-up but not at baseline were categorized as incident BMLs. Hip BMLs present at both baseline and follow-up were categorized as persistent BMLs.

Lastly each 1 cm² change in acetabular BML size was associated with a decrease in total hip and femoral neck BMD: β : -0.01, 95%CI: -0.03, -0.004 and β : -0.01, 95%CI: -0.03, -0.001 respectively. Whereas per 1 cm² increase in femoral BML size was positively associated with increase in femoral neck BMD: β : +0.03, 95%CI: +0.00, +0.05.

Discussion

Hip BMLs were associated with local (total hip and femoral neck) BMD, but not distant BMD (spine). Furthermore, these associations vary according to site with femoral BMLs being associated with higher femoral neck BMD while acetabular BMLs are associated with lower hip and femoral neck BMD. The findings were consistent although not all were statistically significant.

The relationship between BMD and OA has been investigated.²⁰¹ Of these, only a few focus on the role of BMLs and bone density. Population based studies in both participants with and without OA suggests that those with knee BMLs have higher local subchondral BMD.^{202, 203} Further, knee BMLs are associated with increased bone density of the compartment where they are located. It is unclear whether this is due to BMLs having a local effect on bone or whether they are consequences of changes in underlying bone pathology. Demineralization of the bone under or adjacent to the BMLs could be explained by histological studies that suggest BMLs consist of elevated cytokines and angiogenic factors which leads to higher bone turnover locally, hence lower BMD.^{63, 97}

At the hip, due to lack of data, the effects of BMLs on bone density or vice versa is currently unclear. One study reports osteoporosis in 4/8 resected femoral heads with hip BMLs but no correlation was found between this histopathological finding and hip BMLs,¹⁰¹ however OA bone has been found to be hypo-mineralized with increased levels of water and organic materials.³⁹ In our study, femoral BMLs were associated with an increase in bone density. Longitudinally, resolving femoral BMLs were associated with decreasing and incident femoral BMLs were associated with increasing femoral neck BMD. Femoral BMLs would have been located in the similar or exact region in which total hip BMD was assessed. Conversely, acetabular BMLs that are adjacent but outside the region used to assess BMD, were associated with lower BMD. Cross-sectionally there was an estimated 5-6% decrease in

total hip and femoral neck BMD. Longitudinally, bone density was higher in subjects with resolving acetabular BMLs, while a 1% reduction in BMD from baseline to follow-up was noted in subjects with enlarging acetabular BMLs. These findings demonstrate opposite associations for acetabular and femoral BMLs with BMD and should be regarded as hypothesis generating. For instance, overall increase in BMD and bone porosity in subjects with OA and BMLs has been documented.^{63, 202} Additionally, femoral neck BMD in comparison to other locations at the hip is highest in early and severe radiographic hip OA.²⁰¹ It could be speculated that femoral BMLs located near the femoral neck may increase due to an increase in femoral neck BMD or because of changes in the subchondral bone due to increase in bone infiltrates.³⁹ In contrast, acetabular BMLs that are located away from the femoral neck and the subchondral bone associate with a bone undergoing demineralization. Hence, unlike the knee, hip BMLs located in two different compartments might represent bone areas undergoing different pathological changes leading to variations in the bone density adjacent to that joint. Nevertheless, these results might differ if we were able to measure material bone density.

It's unclear if BMLs are the cause or effect of secondary mechanisms modifying the bone. Hip BMLs, in this study, were associated with changes in local BMD perhaps, due to continuous bone remodeling and/or bone reabsorption in bone areas with BML. Studies have found elevated bone biochemical markers such as bone alkaline phosphate (ALP), osteocalcin (OC), and increase in angiogenesis factors such as vascular endothelial growth factor (VEGF), cysteine-rich angiogenic inducer 61 (CYR61), in bone samples with BMLs, suggesting increased bone turnover.⁹⁷ Moreover, BMLs may also reflect a paracrine effect of proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1 (IL-1) and leptin, which associate with pain,²⁰⁵ cartilage loss¹⁴¹ and lower bone density in subjects with OA.^{206, 207} Lastly, bone density may alter due to disuse of a painful joint mainly due to unloading which encourages reduction in bone formation or modeling.²⁰⁸ Hence, both imbalances in the bone metabolism and disuse due to pain possibly cause changes in bone that encourage formation of BMLs.

Limitations

Bone density was measured using DXA, which provides an aerial two-dimensional BMD measure; hence our apparent BMD findings might differ from material BMD findings. As BMD can be influenced by differences in bone size we adjusted for age, sex and BMI, which would largely compensate for any such differences. We were unable to vary the region of interest for our scans thus the region of interest where BMD was measured may include all, part or none of the hip BMLs depending on the location of the BML which may explain differing regional results. Longitudinal analyses were carried out with only a small number of hip BMLs, however the overall results were consistent. Hip BMLs were assessed by both presence and cross-sectional area, which might miss very small shallow or flat BMLs. However, our areal measure has excellent performance metrics in the knee.^{[107](#)}

Conclusions

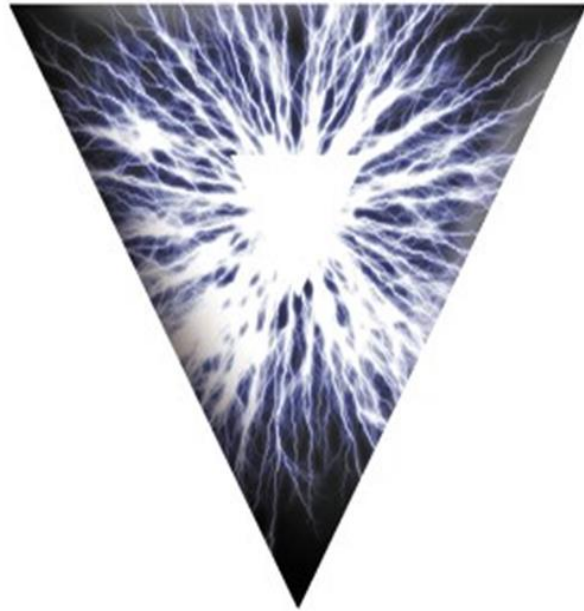
Hip BMLs were associated with local BMD (hip and femoral neck) but not with spine BMD and these associations vary according to site. BML prevalence and change was low in this study, hence these findings need confirmation. However, we hypothesize that these associations represent a combination of changes related directly to the BML pathology or changes adjacent to the disease process.

Postscript

A link between hip BMLs and local BMD (hip and femoral neck) was established in this chapter. At the hip, the association between BMLs and BMD may vary according to the site. As expected, no association between hip BMLs and spine BMD was found. Hypothetically these associations may represent a combination of changes related directly to the BML pathology or changes adjacent to the disease process.

After demonstrating associations of subchondral hip BMLs, the next chapter describes the link between hip cartilage, clinical symptoms and structural changes occurring in older adults.

Chapter 6 : Correlates of hip cartilage defects: A cross-sectional study in older adults.



Published in the Journal of Rheumatology (*in press*)

Harbeer Ahedi, Dawn Aitken, Leigh Blizzard, Chang-hai Ding,

Flavia Cicuttini and Graeme Jones

Now published in vol. 43(7), 1406-1412

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partial thickness defect and grade 2=full-thickness defect with bone ulceration and/or exposure of bone. If more than one defect was present at one site, the highest score was used. In a reliability study of 40 subjects with re-measurements after four weeks, the intra-rater agreement (kappa) was 0.89.

Furthermore, the inter-rater reliability (kappa) assessed by two readers (n=40) for presence of defects and defect categories was 0.84 and 0.63 respectively. These measures were conducted by HA and ML (Ming Lu). ML is an orthopedic surgeon with 7 years' experience in reading MRI scans.

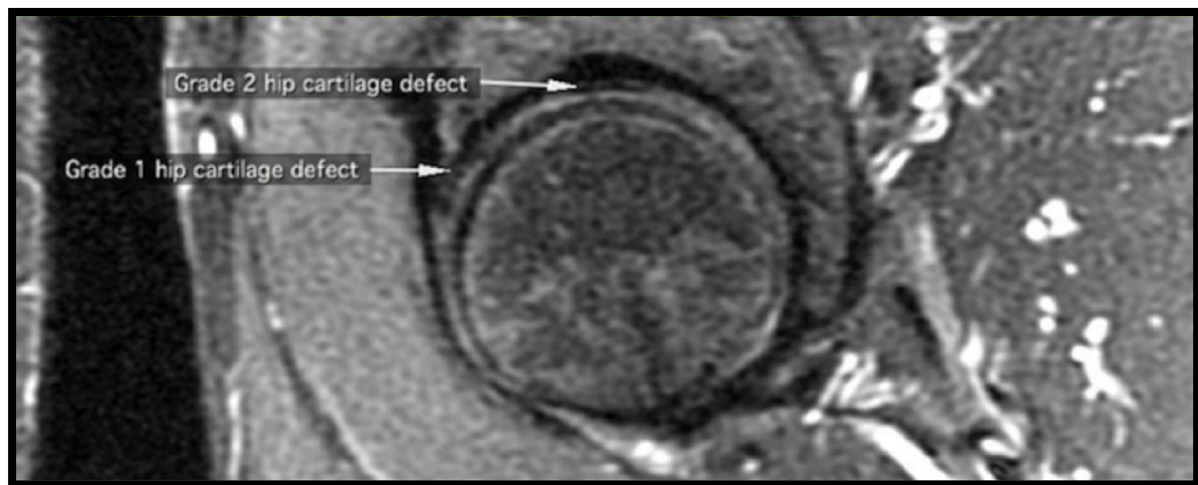


Figure 6-1: Assessment of grade 1 and grade 2 hip cartilage defects on sagittal STIR MRI image

Assessment of hip effusion

Hip joint effusion was assessed manually by one observer (HA). HA selected the MRI slice with the largest effusion and then assessed the maximum cross-sectional area (CSA). The intra-rater agreement (kappa), for presence of hip effusion was 0.84 and the intra-class correlation coefficient (ICC) for hip effusion CSA was 0.97.

Hip BMLs and high cartilage signal

BMLs were identified as areas of increased signal intensity adjacent to the subchondral bone on the femoral head and/or the acetabulum and maximum BML CSA was assessed. The ICC for hip BMLs was 0.98.²¹⁵ High cartilage signal was defined as a high signal intensity band

within the cartilage either adjacent to a hip BML or at any location on the STIR MRI slice if there was no BML present. High cartilage signal was graded as 0 for absent and 1 for present with an intra-rater agreement (Kappa) of 0.88.²¹⁵

Radiological assessment

Antero-posterior weight-bearing radiographs of the pelvis were obtained. According to the OARSI (Osteoarthritis Research Society international) grading system, the radiographic features of JSN and osteophytes of the right hip were graded on a 4-point scale, ranging from 0 to 3 where 0=no disease and 3=most severe disease by using an Altman's atlas.⁷⁷ The total radiographic OA(ROA) score was calculated by summing the JSN and osteophyte scores.⁸⁶ A non-zero score of either JSN or osteophytes was regarded as evidence of hip ROA. Thus, after combining JSN and osteophytes score, the presence of hip ROA was defined as a total score of 1 or greater.

Statistical analyses

Student's t-test and chi-square tests were applied to determine the differences in means and proportions. Based on total WOMAC score which ranged from 0-45, hip pain was divided into three categories: category 0 comprised subjects with no pain, category 1 comprised subjects with pain score less than 4, and category 2 comprised subjects with pain score of at least or more than 4. Hip BMLs and effusion were dichotomized as 0=no BML/effusion and 1=BMLs/effusion>0. Log binomial regression (a generalized linear model with log link and binomial error) was used to estimate associations with the binary outcome hip cartilage defects. Linear regression was employed to estimate associations with continuous outcomes. All models were adjusted for age, body mass index and hip BML (as required) because these factors produced at least 10% of change in the coefficient of the study factor. Results are presented stratified by sex (when the interaction of study factor with sex was statistically significant) or additionally adjusted by sex. Data on subjects at phase 2 and phase 3 were combined in analyses (194 subjects with MRI at both phases), and the correlation between repeated measurements on individuals was taken into account by adjusting standard errors using the sandwich (robust) estimator of variance.^{189, 190} An assessment was made of the fit of all the final models, with careful attention paid to the scaling of covariates and of the response variable in linear regression. Intra-rater and inter-rater reliability was computed using

weighted (w) kappa. All statistical tests were two sided and p values < 0.05 were considered significant.

Results

Characteristics of the sample population

Table 6-1 summarizes the characteristics of the subjects with no defect, grade 1 and grade 2 defects. Overall, 24% (n=48) subjects had no cartilage defects, 34% (n=66) had grade 1 and 41% (n=80) had grade 2 cartilage defects. When a significant sex interaction was found, the data was stratified into men and women. In comparison to those with no cartilage defects, subjects with a grade 1 defect were of similar age, but heavier. Men with grade 1 defects had more hip pain and an increased proportion of high cartilage signal. Regardless of sex, subjects with grade 1 defects had more hip BMLs. In comparison to subjects with no defects, those with grade 2 defects had similar BMI but were older; and had a higher hip pain score, higher proportion of hip BMLs and high cartilage signal, larger effusion CSA and lower steps per day. The proportion with hip ROA in those with grade 2 cartilage defects was higher in men than in women.

Table 6-1 Characteristics of the sample population

Characteristics	Hip defect absent (n=48)	Grade 1 hip defect present (n=66)	<i>P-value</i>	Grade 2 hip defect present (n=80)	<i>P-value</i>	Table 6-1: Characteristics of the sample population
Age (yrs.): mean (SD)	64.1 (6.73)	64.1 (6.84)	0.95	65.5 (7.70)	0.01	
BMI (kg/cm ²): mean (SD)	27.2 (3.99)	28.2 (4.43)	0.02	27.5 (4.20)	0.53	
Hip pain [†]						
Presence [‡]	40%	48%	0.14	46%	0.81	
Men	22%	44%	0.002	-	-	
Women	62%	53%	0.2	-	-	
Interaction <i>p-value</i>		<i>p=0.003</i>				
Severity: § mean (SD)	1.32 (3.14)	2.10 (4.20)	0.07	2.60 (5.11)	0.03	
Leg strength (kgs): mean (SD)	101 (53.0)	99 (53.0)	0.71	98.0 (48.7)	0.73	
Steps per day: mean (SD)	7970 (3526)	7444 (3245)	0.15	7127 (3507)	0.04	
Any BML	5%	20%	0.003	23%	0.009	
Presence of high cartilage signal	42%	60%	0.002	62%	0.009	
Men	40%	70%	<0.001	-	-	
Women	44%	46%	0.81	-	-	
Interaction <i>p-value</i>		<i>p=0.008</i>				
Hip Effusion [†]						
Presence [¶]	10%	18%	0.07	20%	0.09	
Effusion CSA: ** mean (SD)	1.05 (0.79)	1.16 (0.96)	0.31	1.30 (1.01)	0.02	
Presence of radiological hip OA	28%	30%	0.94	40%	0.002	
Men	22%	-	-	50%	0.001	
Women	27%	-	-	27%	0.97	
Interaction <i>p-value</i>		<i>p=0.007</i>				

Results of t-tests (continuous variables) and chi-squared tests (categorical variables), with standard errors of means calculated with clustering of observations on subjects at phase2 and phase3 taken into account. Two-way Anova test was used for estimating sex interactions. †Pain score calculated using Western Ontario and McMaster Universities Osteoarthritis index (WOMAC). ‡ Presence of hip pain defined as grade 0= no hip pain and grade 1= pain score>0.

§ For subjects with hip pain score >0. ¶ Presence of hip effusion has been dichotomized as grade 0 = no effusion or/and effusion CSA ≤ 2.0 cm² and grade 1= effusion ≥ 2.0 cm². **Mean effusion and standard deviations have been obtained by using t-test including only subjects with effusion CSA>0.

Categories of hip pain and hip defects

Table 6-2 presents the cross-sectional associations between categories of hip pain and hip cartilage defects. Those with higher hip pain had greater prevalence of any and grade 2 defects, but grade 1 defects were not associated with either categories of hip pain.

Table 6-2: The cross-sectional associations between categories of hip pain and hip cartilage defects.

	Any hip defect	Grade 1 defects	Grade 2 defects
Hip pain	PR (95%CI)	PR (95%CI)	PR (95%CI)
Category 0	1.00	1.00	1.00
Category 1	1.00 (0.83, 1.20)	1.04 (0.77, 1.40)	0.96 (0.70, 1.40)
Category 2	1.20 (1.02, 1.35)	1.22 (0.93, 1.60)	1.40 (1.09, 1.80)

Independent variable: hip cartilage defects. Dependent variable: Hip pain category.

Hip pain category 0 includes subject with no pain.

Hip pain category 1 includes subjects with >0 & < 4 hip pain score.

Hip pain category 2 includes subjects with ≥ 4 hip pain score.

†PR (95%CI) = prevalence ratios (95% confidence intervals) adjusted for age, sex and body mass index and with clustering of observation on subjects at phase 2 and phase 3 taken into account.

Structural abnormalities and grade 1 cartilage defects

Table 6-3 summarizes the cross-sectional associations between structural abnormalities and grade 1 cartilage defects stratified by sex. The prevalence and size of hip BMLs was greater in men but no sex interaction was found. Similarly, an association between high cartilage signal and grade 1 defect was found in men, but not in women. Other abnormalities such as hip effusion and radiological aspects were not associated with grade 1 defects.

Table 6-3: Cross-sectional associations between structural abnormalities and grade 1 cartilage defects stratified by sex.

	Men	Women	<i>P value for interaction</i>
	Hip defect present	Hip defect present	
Study factor	PR (95% CI) *	PR (95% CI) *	
MRI abnormalities			
Any hip BMLs (Y/N)	1.42 (1.03, 1.96)	1.20 (0.80, 1.76)	0.50
Hip BML CSA [‡]	1.41 (1.11, 1.71)	1.25 (0.81, 1.68)	0.56
High cartilage signal (Y/N) [†]	1.80 (1.04, 2.53)	0.92 (0.63, 1.22)	0.01
Hip effusion (Y/N)	1.03 (0.60,1.83)	0.83 (0.60,1.20)	0.52
Hip effusion CSA [‡]	1.00 (0.83, 1.21)	1.08 (0.88, 1.30)	0.40
Radiological abnormalities			
Radiological hip OA (ROA) (Y/N)	1.20 (0.80,1.82)	0.90 (0.60, 1.44)	0.41
Joint Space Narrowing (JSN) (Y/N)	1.12 (0.62, 2.03)	0.80 (0.44, 1.41)	0.40
Osteophytes (OST) (Y/N)	0.90 (0.50, 1.60)	1.20 (0.73, 1.88)	0.44

Independent variable: structural abnormalities. Dependent variable: presence of hip cartilage defect

*PR (95%CI) = prevalence ratios (95% confidence intervals) adjusted for age, sex and body mass index and with clustering of observation on subjects at phase 2 and phase 3 taken into account.

[†]PR (95%CI) = prevalence ratios (95% confidence intervals) further adjusted for presence of hip BMLs.

[‡]CSA= cross-sectional area.

Structural abnormalities and grade 2 cartilage defects

Table 6-4 presents the cross-sectional associations between structural abnormalities and grade 2 cartilage defects. In these analyses, subjects with grade 2 cartilage defects had a higher prevalence of hip BMLs and larger hip effusion size compared to subjects with no cartilage defects. Those with grade 2 defects also had a higher prevalence of high cartilage signal (PR: 1.30 95%CI: 1.03, 1.62) but this association became non-significant after adjusting for hip BMLs. The link between grade 2 defects and radiological hip OA was only present in men.

Table 6-4: Cross-sectional associations between structural abnormalities and grade 2 cartilage defects

Study factor	Hip cartilage defect PR (95% CI) *
MRI abnormalities	
Any hip BMLs (Y/N)	1.45 (1.15, 1.85)
Any hip BML CSA [‡]	1.42 (1.21, 1.66)
High cartilage signal (Y/N) [†]	1.20 (0.95, 1.52)
Hip effusion (Y/N)	0.98 (0.65, 1.50)
Hip effusion CSA [‡]	1.14 (1.01, 1.30)
Radiological abnormalities	
Radiological hip OA (ROA) (Y/N)	1.30 (0.96, 1.70)
Men	1.60 (1.13, 2.25)
Women	0.80 (0.45, 1.40)
<i>Interaction (p-value)[¶]</i>	<i>p=0.04</i>

Independent variable: structural abnormalities. Dependent variable: presence of hip cartilage defect

*PR (95% CI) = prevalence ratios (95% confidence intervals) adjusted for age, sex and body mass index and with clustering of observation on subjects at phase 2 and phase 3 taken into account.

[†]PR (95% CI) = prevalence ratios (95% confidence intervals) further adjusted for presence of hip BMLs.

[‡] CSA= cross-sectional area.

Steps per day and grade 2 cartilage defects

Table 6-5 presents the cross-sectional relationship between steps/day and grade 2 cartilage defects. Steps/day and its categories were associated with a lower prevalence of grade 2 defects. These associations persisted after adjustment for age (using the residual method).

Table 6-5: Cross-sectional relationship between steps/day and grade 2 cartilage

Study factor	Grade 2 hip cartilage defects
	PR (95% CI)*
Steps/ day	0.97 (0.96, 0.99)
Steps/day categories	
0-5000 steps	1.00
5000-7499 steps	0.90 (0.77, 1.04)
7500-9999 steps	0.87 (0.74, 1.01)
10,000+ steps	0.77 (0.65, 0.91)
Independent variable: Steps per day and steps per day categories. Dependent variable: grade 2 hip cartilage defects.	
*PR= prevalence ratios with 95% confidence intervals, adjusted for age residuals, sex and body mass index and with clustering of observations on subjects at phase 2 and phase 3 taken into account.	

defects

Any hip defects and leg strength

Figure 6-2 presents the association between any hip defects and leg strength stratified by sex. Presence of any hip defect was associated with lower leg strength among men (mean ratio: 0.83 95%CI: 0.67-0.98), but not women (mean ratio: 0.91 95%CI: 0.80-1.03).

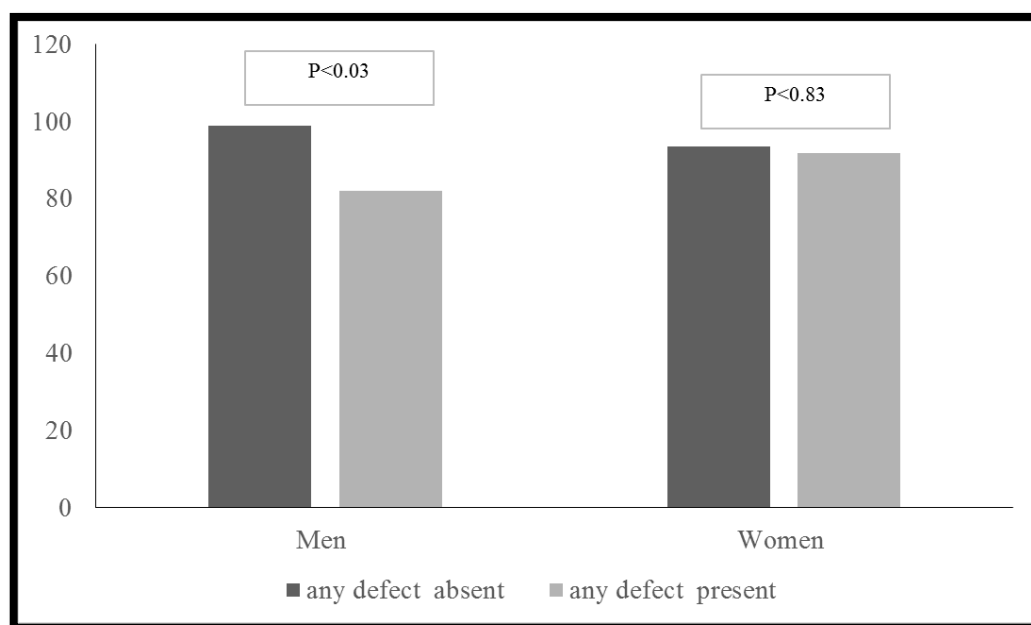


Figure 6-2: Association between any hip cartilage defects and leg strength stratified by sex.

Independent variable: leg strength. Dependent variable: Presence of any hip cartilage defects. Data adjusted for age, body mass index and with clustering of observations on subjects at phase 2 and phase 3 taken into account.

Discussion

This is the first population-based study that describes the correlates of hip cartilage defects and these associations are similar to knee defects. Overall, 76% of the population had hip cartilage defects and correlates of hip defects, in this cohort, appeared to be somewhat influenced by sex. Any hip cartilage defects associated with greater hip pain and men with any defects had lower leg strength. Associations of grade 1 hip cartilage defects were restricted to high cartilage signal (men only) and hip BMLs. Grade 2 cartilage defects were not only associated with higher hip pain, hip BMLs but also with hip effusion size and hip ROA (men only). Steps per day was protective of grade 2 cartilage defects.

In unadjusted analyses (table 6-1), presence of hip pain and hip pain severity was greater in subjects with grade 1 and grade 2 hip cartilage defects, respectively. In the multivariable analyses, any and grade 2 hip cartilage defects were associated with pain category 2 while grade 1 showed no such associations. Hip cartilage defects were not associated with hip pain category 1. In this study, hip pain was categorized using a cutoff point of 4. Earlier studies have used clinically relevant cut off points^{219, 220} and as presumed, those with higher pain score had greater prevalence of cartilage defects. An MRI based study validating a hip osteoarthritis score found higher odds of hip pain in those with hip cartilage defects but these analyses were not statistically significant.⁹³ Subsequently, a case-control study of 85 subjects with mild to moderate hip OA, demonstrated a modest correlation between acetabular defects and hip pain ($r = -0.25$, $p < 0.02$).¹¹² Although different methods were applied to classify defects, our findings are consistent with these studies. For instance, *Roemer et.al* classified defects into grade (0-3) and *Kumar et.al* and *Teichtahi et.al* classified defects into grade (0-2 and 0-1 resp.) by sub-regions of the femoral head/acetabulum on MRI images.^{93, 112, 136} We categorized hip defects as grade (0-2) and found similar results. In addition, our data implies that those with greater cartilage damage may have higher probability of hip pain.

The association between hip defects and leg strength is a novel finding. We found that men with hip cartilage defects had lower leg strength. No other study has explored this concept at the hip but some data exists for the knee.^{213, 221} In 87 women, knee

cartilage damage in combination with either pain or presence of loose bodies explained 28-38% of the variation in isokinetic extension strength. In women with knee cartilage damage, synovitis and/or effusion explained 34% variability in isometric flexor strength.²¹³ In both men and women with lower quadriceps muscle strength, there was a greater prevalence of patella-femoral cartilage damage.²²² The dynamometer used in the TASSOAC study predominantly captures quadriceps and hip extensor strength. The associations between leg strength and hip cartilage defects were predominately seen in men, but are similar to the above studies. Our results suggest that hip cartilage defects (like knee defects) associate with muscle strength. However, longitudinal studies are required to assess cause and effect. Age adjusted steps/day and doing +10,000 steps/day was associated with a lower prevalence of grade 2 cartilage defects. Any or grade 1 cartilage defects showed no such associations (data not shown). This concept has not been examined at the hip and the evidence for knee is controversial. For instance, in an asymptomatic sample, 93% of subjects with a high level of physical activity had knee cartilage lesions.²²³ A longitudinal study demonstrated that subjects with a knee BML at baseline and doing 10,000+ steps/day were more likely to have worsening knee cartilage damage.¹⁵³ Another longitudinal study showed physical work capacity was modestly and positively correlated with knee bone area but negatively with knee cartilage volume.²²⁴ Here, physical activity associated with lower prevalence of grade 2 hip cartilage defects. Again, longitudinal studies are required and there is a possibility that subjects with grade 2 defects take less number of steps per/day due to hip pain. Due to the lack of consistency in evidence and no other comparable data at the hip, it is hard to define at this point if physical activity is helpful or harmful for hip cartilage.

Subjects with a hip BML had approximately 1.5 times higher risk of having a grade 1 or grade 2 hip cartilage defects. BMLs have gained much attention and play a key role in OA. At the hip, studies have reported hip BMLs, articular damage and cartilage defects in subjects with and without symptomatic hip OA but these did not document associations between BMLs and cartilage defects.^{93, 101, 214} *Neumann et.al*, demonstrated a strong positive correlation between hip defects and hip BMLs($r=0.44$, $p<0.001$) in subjects with and without hip OA.¹³⁵ While *Register et.al* found a positive correlation between hip chondral defects and acetabular BMLs($p=0.009$) in asymptomatic subjects with hip structural changes.²¹⁴ Our study is consistent with

these findings and demonstrates associations between hip BMLs and defects in a community-based sample.

Men with a high cartilage signal were 80% more likely to have a grade 1 defect; while, men and women with a high cartilage signal were 30% more likely to have a grade 2 defect (PR:1.30 95%CI:1.03,1.62). However, this association became non-significant after adjusting for hip BMLs. The significance of high cartilage signal intensity has been described at the knee.^{122, 124, 128, 225} Our group was the first to outline its association with hip BMLs²¹⁵ and in this study we demonstrated its association with grade 1 defects further validating its role as an early marker for cartilage changes. Its association with grade 2 hip cartilage defect was not independent of hip BMLs. Thus, the association of high cartilage signal with grade 2 cartilage defects is mediated by hip BMLs, indicating a possibility of an underlying causal pathways between these structural changes.²¹⁵

Hip effusion CSA was associated with grade 2 defects and these subjects had 14% larger hip effusion. Presence of hip effusion did not associate with hip cartilage defects. Joint effusion at the knee has been linked with progression of cartilage defects²¹⁶ but its role in hip OA has not been reported. Joint effusion is an inflammatory process and may directly affect the cartilage matrix or could be a consequence of cartilage damage.¹¹⁵ Either way, our findings support this hypothesis.

In the current study, men with radiological changes were 60% more likely to have grade 2 hip defects. Grade 1 or any hip defects were not associated with hip ROA. Radiological changes at the hip are part of the diagnosis of hip OA,^{93, 112, 226} but less is known about its relationship with hip defects. Earlier studies reported greater cartilage damage with increasing KL-grade in subjects with severe hip OA.⁹³ Furthermore, worsening KL-grade was associated with femoral ($r=0.33$, $p=0.002$) and acetabular defects ($r=0.34$ $p=0.001$).¹¹² Our data is highly consistent with both these studies; however, the association between ROA and defects was stronger in men than women.

Limitation

This study has some potential limitations. The analyses are cross-sectional. Assessing hip cartilage is challenging and the technique used to assess hip defects was adapted from earlier studies.¹²⁶ We acknowledge that we are unable to provide arthroscopic or pathological validation and those with defects are at a higher risk of OA but having a defect may not be a precursor for hip OA. During measurements, it is possible we might have missed a small or shallow cartilage defect. However, our reproducibility was high, our previous measures have shown excellent measurement metrics and as hypothesized our findings are consistent with earlier studies at the knee and the hip. Lastly, the MRI sequence utilized could not separate synovitis from effusion and associations may vary if each is examined separately.

Conclusion

In conclusion, grade 2 defects in both sexes and grade 1 (mostly in men) are associated with clinical, demographical and structural factors relevant for OA. Damage to the hip cartilage could one of the major causes of rapid disease progression and pathophysiology of hip defects needs further study.

Postscript

The results from this chapter reveal that greater hip cartilage damage was associated with hip pain, BMLs, hip effusion, change in high cartilage signal and radiological findings. Furthermore, physical activity was associated with lower prevalence of hip cartilage defects and men with hip cartilage defects had lower leg strength. In general, correlates of hip cartilage defects are extensive and may lead to rapid disease progression.

The aim of the next chapter is to describe the cross-sectional and longitudinal associations of hip effusion-synovitis in older adults.

Chapter 7 : Hip effusion-synovitis and it's cross-sectional and longitudinal associations with hip pain, cartilage damage, subchondral BMLs and early radiographic hip OA.



This chapter is under peer review in APLAR Journal of Rheumatology.

Harbeer Ahedi, Dawn Aitken, Leigh Blizzard,

Flavia Cicuttini and Graeme Jones

Introduction

Osteoarthritis (OA) is characterized by alterations in composition, structure, and function of the various components of joint, including synovium.^{115, 116, 139} OA has been historically categorized as non-inflammatory arthritis.¹³⁹ However, synovitis plays a key role in cartilage damage and vice versa.^{116, 139} Occurring in either early or late stages of OA, synovitis leads to increase in catabolic and proinflammatory mediators such as cytokines, nitric oxide, prostaglandin E, and neuropeptides. These mediators produce excess proteolytic enzymes, which cause cartilage matrix degradation. In turn, cartilage breakdown leads to worsening synovitis.¹³⁹

Joint effusion can be visually distinguished from synovitis using contrast-enhanced MRI. However, it has potential side effects and is not economical. Recently, the term 'effusion-synovitis' has been proposed for effusion and synovitis because these two features cannot be differentiated by non-contrast MRI.¹⁴³

Several types of studies, including MRI-based studies have reported associations of knee effusion-synovitis proving that it is one of the causes of knee pain, has an adverse effect on cartilage and is linked with radiographic knee OA.^{115, 134, 144-146} Although synovitis-effusion is a significant clinical prognostic factor for OA, at the hip it remains under-investigated.

A small retrospective study was the first to report hip effusion in 12/12 subjects and severe synovitis in 9/12 subjects with hip RDOA (Rapidly Destructive OA) but did not demonstrate correlations of hip effusion.¹⁰² Subsequently, in a clinical study, hip effusion-synovitis was reported in 70% of the subjects and major or/and asymmetrical hip effusion-synovitis associated not only with hip pain but also with hip radiographic OA (ROA).¹⁴⁷ In an MRI-based study evaluating hip effusion and synovitis separately, a weak association between grade 1 synovitis (but not grade 2) and hip pain was found. However, in subjects with either synovitis or effusion, severe hip ROA was prevalent.⁹³ In a retrospective study, extensive synovitis was found in subjects with RDOA than in those with hip OA, indicating that higher synovitis could be related to rapid disease progression.²²⁷ Similar and modest correlations between

synovitis-effusion and hip ROA were demonstrated in a recent study validating a scoring system to evaluate hip OA. However, there was no association between hip effusion-synovitis and hip pain score.⁹⁴

Effusion-synovitis may be associated with hip ROA and only one study reports its association with hip pain. To the best of our knowledge, a population-based longitudinal study examining hip effusion-synovitis has not been published. Given the impact of synovitis on the joint and cartilage, examining effusion-synovitis should be one of the primary focuses for research in OA. Such information could be beneficial to generate techniques to target effusion-synovitis for management and control of OA and also for preserving the cartilage and reducing pain. Hence, this study aims to describe the cross-sectional and longitudinal associations of hip effusion-synovitis in a large community-based sample.

Methods and Materials

Subjects

The Tasmanian Older Adult Cohort (TASOAC) study is an ongoing prospective, population-based study initiated in 2002 and has been extensively described in previous studies.¹⁰⁷ The current study is a sub-sample from the TASOAC cohort. During the TASOAC study, a hip protocol was added during the latter part of phase 2. A sample of 245 consecutive participants who had a STIR (Short T1 Inversion Recovery) MRI sequence at phase 2 and/or phase 3 were included. Of these 245 participants, 30 participants were lost to follow-up in phase 3 and 17 subjects had no STIR MRI at phase 2. Of 198 subjects, hip effusion-synovitis could not be adequately assessed in the MRI scans of 2 subjects and these were excluded. Accordingly, a total of 196 subjects with complete data were included in this study. Written informed consent was obtained from all participants and the Southern Tasmanian Health and Medical Human Research Ethics Committee approved this study.

Clinical and hip pain measures

Height, weight and body mass index (BMI) were measured using standard protocol. Hip pain for all the subjects was determined using a hip specific Western Ontario and McMaster Universities Arthritis Index(WOMAC).⁸⁹ WOMAC uses a ten-point scale from 0(indicating no pain) to 9(indicating severe pain). Hip pain(five items) was assessed using the following questions: ‘Referring to your hips only, how much pain did you experience when walking on flat surface, going up and down the stairs, at night while in bed, sitting or lying, and standing upright.’ These five items were summed to create a total hip pain score, each with a possible range from 0 to 45

Magnetic Resonance Imaging (MRI)

The right hip was imaged in the sagittal plane using a 1.5 Tesla G.E signal whole-body magnetic resonance unit with a phased-array flex coil. The following image sequence was used: STIR-weighted fat saturation two-dimensional fast spin echo sequence; repetition time 4340 msec, echo time 28.4 msec; field of view 20 cm; 15 partitions and 512 x 512-pixel matrix. Sagittal images were obtained at a slice thickness of 3.5 mm with an interslice gap of 1.5mm.

Quantitative assessment of hip effusion-synovitis

For quantitative measurements of hip effusion-synovitis, the observer (HA) selected the MRI slice with the largest effusion-synovitis and measured the maximum cross-sectional area (CSA) by drawing contours around the outer edges (Figure 1). If the effusion-synovitis was present at more than one site around the femoral head (anterior, posterior or both), then the largest CSA of effusion-synovitis on each site was assessed. The reproducibility was evaluated in 40 subjects, with a four weeks’ interval between the two measures. The intra-rater agreement (kappa) for the presence of hip effusion-synovitis was 0.84, and the intra-class correlation coefficient (ICC) for hip effusion-synovitis CSA was 0.97.

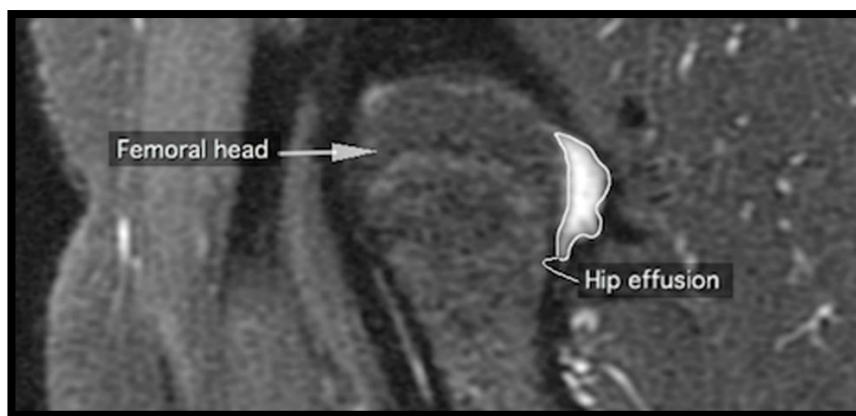


Figure 7-1: Assessment of hip effusion-synovitis using OsiriX imaging software

Assessment of hip cartilage defects, hip BMLs, and high cartilage signal

Hip cartilage defects were assessed using OsiriX (Figure 2). Hip defects were identified as any change in the hip cartilage and were categorized as; grade 0=normal cartilage, grade1=focal blistering or irregularities on the cartilage surface or a partial thickness defect and grade2=full-thickness defect with bone ulceration and/or exposure of bone. If a hip cartilage defect was located at the femoral head, it was labelled as femoral cartilage defect and if a hip cartilage defect was located at the acetabulum it was labelled as acetabular cartilage defect. If more than one defect was present at one site, the highest score was used. In a reliability study of 40 subjects with re-measurements after four weeks, the intra-rater agreement (kappa) was 0.89. Furthermore, the inter-rater reliability (kappa) assessed by two readers (n=40) for the presence of hip cartilage defects and defect categories was 0.84 and 0.63 respectively (Figure 7-2).

Hip BMLs were identified as areas of increased signal intensity adjacent to the subchondral bone on the femoral head and/or the acetabulum. The observer manually selected the MR slice with the largest BML and then determined the BML size (cm²) (Figure 7-2).²¹⁵ High cartilage signal intensity change^{122, 128} was defined as a high signal intensity band within the hip cartilage either adjacent to a hip BML or at any location on the STIR MRI slice if there was no BML present (Figure 7-2).²¹⁵

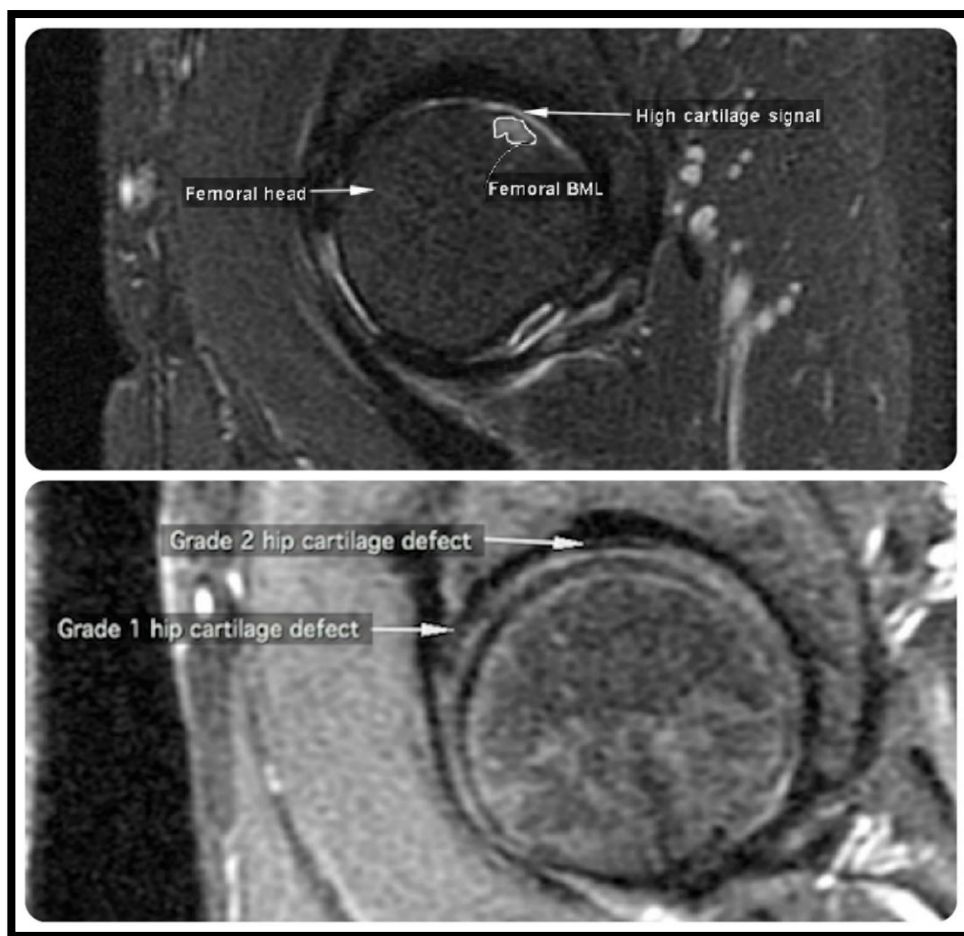


Figure 7-2: Measurement of hip BML, high cartilage signal and hip cartilage defects using OsiriX imaging software

Hip radiographs

Antero-posterior radiographs of the pelvis with weight bearing and with both feet in 10 degrees internal rotation were obtained and radiographs were assessed for radiographic hip OA at phase 1 (baseline). All images were scored for joint space narrowing (JSN) and osteophytes, each on the scale of 0-3 (0=normal and 3=severe) according to the Osteoarthritis Research Society International(OARSI) atlas.⁷⁷ The JSN and osteophytes scores were summed to produce a hip total radiographic score and a total score of greater than 1 is defined as presence of hip ROA.⁸⁶ A non-zero score of either JSN or osteophytes was regarded as evidence of hip ROA. Thus, after combining JSN and osteophytes score, the presence of hip ROA was defined as a total score of 1 or greater.

Statistical analyses

Ninety-four percent of the population had any hip effusion-synovitis. We were unable to differentiate between physiological (e.g. normal joint fluid) and pathological joint fluid. Initial data driven cut off points did not reveal any significant results. For some analyses, the population was divided into two groups by median effusion-synovitis CSA. The first group included subjects with no or small ($<0.77\text{cm}^2$) hip effusion-synovitis and the second group included subjects with moderate or large hip effusion-synovitis ($\geq 0.77\text{cm}^2$). Within these two groups, differences in demographical characteristics were calculated by using unpaired t-tests and chi-square tests (Table 7-1). Hip effusion-synovitis was also analysed by the number of sites affected (independent of size) and continuously as CSA.

For cross-sectional analysis, log-binomial regression was employed to estimate the association between presence of hip pain, moderate/large hip effusion-synovitis and presence of hip effusion-synovitis at one or two/three sites. For estimating the relationship between severity of hip pain, moderate/large hip effusion-synovitis and effusion-synovitis at multiple sites, linear regression of the logarithm of pain score on a binary covariate for hip effusion-synovitis was used. Again, log-binominal regression models were applied to investigate the associations between presence of hip BMLs, high cartilage signal, hip cartilage defects, hip ROA and presence of hip effusion-synovitis while linear regression was used to test the relationship between these factors and hip effusion-synovitis CSA. Associations between presence of hip BMLs and presence of hip cartilage defects were also investigated using similar models.

For longitudinal analyses, linear regression models were administered to estimate the relationship between change in hip pain and change in hip effusion-synovitis CSA. Similarly, the association between change in prevalence of hip BMLs, hip cartilage defects, hip ROA (baseline only) and change in hip effusion -synovitis CSA was examined using linear regression. Log binominal regression was employed to investigate if hip BMLs predicted incident and worsening of hip cartilage defects and vice versa (from phase 2 to phase 3). All models were adjusted for age, sex, body mass index (BMI), hip BMLs and hip cartilage defects as required. For cross-sectional analysis only, data on subjects at phase 2 and phase 3 were combined in analyses. All

statistical tests were two sided and p values < 0.05 were considered significant and were conducted using Intercooled Stata 12 for Mac (Stata Corp, College station, TX, USA).

Results

Characteristics of the sample population

Table 7-1 presents the characteristics of the sample population split by the median effusion-synovitis size. Age, the percentage of males and BMI was similar in subjects with no/small and moderate/large hip effusion-synovitis. Presence of hip pain was higher in those with moderate/large hip effusion-synovitis but no other differences were observed between the two groups for structural or radiographic features of the hip.

Table 7-1: Characteristics of the sample population

Characteristics	Small or no hip effusion- synovitis (N=63)	Moderate or large hip effusion- synovitis (N=133)	<i>p-value</i>
Age (yrs.): mean (SD)	64.1 (6.72)	64.7 (7.01)	0.40
Male sex (%)	46%	45%	0.94
BMI (kg/cm ²): mean (SD)	27.6 (4.45)	28.0 (4.40)	0.32
Hip pain			
Presence	30%	38%	0.04
Severity: mean (SD)	1.96 (5.52)	1.98 (4.12)	0.95
High cartilage signal	56%	58%	0.72
Presence of any bone marrow lesions (BMLs)	20%	14%	0.11
Hip cartilage defects			
Femoral defects	52%	60%	0.11
Acetabular defects	66%	66%	0.93
Any hip defects	68%	73%	0.33
Presence of radiographic hip OA (ROA)	50%	53%	0.81

Data presented as means (SD) and proportions.
 Bold indicates statistically significant results ($p < 0.05$).

Cross-sectional associations between hip pain and categories of hip effusion-synovitis

Table 7-2 shows the cross-sectional associations between the presence and severity of hip pain and categories of hip effusion-synovitis. Overall, subjects with moderate/large hip effusion-synovitis had 31% greater hip pain but this association was not statistically significant. Nevertheless, those with hip effusion-synovitis at multiple sites had 42% higher hip pain in comparison to those with hip effusion-synovitis at only one site. Hip effusion-synovitis did not associate with severity of hip pain.

Table 7-2: Cross-sectional associations between presence of hip pain and categories

Study factor	Presence of hip pain	Severity of hip pain
Categories of hip effusion-synovitis	Adjusted PR (95%CI) *	Ratio of means (95%CI) **
Moderate/large hip effusion-synovitis	1.31 (0.98, 1.74)	0.81 (0.53, 1.08)
Hip effusion- synovitis at two/three sites	1.42 (1.05, 1.93)	0.99 (0.70, 1.40)

Independent variable: presence and severity of hip pain. Dependent variable: hip effusion-synovitis (moderate/large & multiple sites)

*PR (95%CI)= prevalence ratios (95% confidence intervals) adjusted for age, sex, BMI, presence of hip BMLs, presence of cartilage defects and with clustering of observation on subjects at phase 2 and phase 3 taken into account.

** Ratio of means (95% confidence intervals) adjusted for age, sex, BMI, presence of hip BMLs, presence of hip cartilage defects and with clustering of observation on subjects at phase 2 and phase 3 taken into account.
of hip effusion.

Cross-sectionally, hip BMLs (PR:0.75 95%CI:0.36,1.60), high cartilage signal (PR:1.01 95%CI:0.85,1.21), hip cartilage defects (PR:1.12 95%CI:0.88,1.42) and hip ROA (PR:0.94 95%CI: 0.74,1.20) were not associated with the presence of hip effusion-synovitis. Nevertheless, any hip BMLs associated with any hip cartilage defects (PR: 1.22 95%CI 1.06, 1.40) independent of presence of hip effusion-synovitis.

For hip effusion-synovitis CSA, independent of presence of hip BMLs, femoral cartilage defects (β : 0.32 95%CI 0.08, 0.56) associated with hip effusion-synovitis CSA. No other structural or radiographic features of hip showed statistically significant associations with hip effusion-synovitis size.

Change in hip pain and change in hip effusion-synovitis CSA

Table 7-3 summarizes the longitudinal association between change in hip pain and change in hip effusion- synovitis CSA. Although, resolving hip effusion showed a reduction in hip pain and worsening or persistent hip effusion- synovitis showed an increase in hip pain but these analyses were not statistically significant.

Table 7-3: Longitudinal associations between change in hip pain and hip effusion-

Study factor		Change in hip pain	Change in hip pain
	n	Adjusted	Further adjusted
		<i>beta</i> (95% CI)*	<i>beta</i> (95% CI)**
No hip effusion- synovitis	8		
Resolved hip effusion- synovitis	11	-0.20 (-1.51, 1.20)	-0.31 (-1.82, 1.20)
Worsening or persistent hip effusion -synovitis	174	+0.32 (-0.81, 1.46)	+0.30 (-0.91, 1.52)

Independent variable: change in hip pain. Dependent variable: change in hip effusion-synovitis CSA/size

**beta* co-efficient (95% confidence intervals) adjusted for age, sex and body mass index and with clustering of observation on subjects at phase 2 and phase 3 taken into account.

** *beta* co-efficient (95% confidence intervals) further adjusted for hip BMLs and hip cartilage defects at phase 2.

Bold indicates statistically significant results.

CSA= cross-sectional area

Change in prevalence of structure abnormalities and change in hip effusion-synovitis CSA

Table 7-4 outlines the longitudinal associations between change in prevalence of any large hip BMLs, hip cartilage defects, hip ROA (baseline) and change in hip effusion-synovitis CSA. Any large persistent hip BMLs and incident of hip cartilage defects was associated with an increase in hip effusion-synovitis CSA. These associations persisted even after adjusting for hip BMLs or hip cartilage defects. However, presence of hip ROA did not show an association with change in hip effusion-synovitis CSA.

Table 7-4: Longitudinal associations between change in hip effusion- synovitis size, structural anomalies and radiographic findings.

Study factor	n	Change in effusion- synovitis CSA	Change in effusion- synovitis CSA
		Adjusted	Further adjusted
		<i>beta coefficient</i> <i>(95%CI)*</i>	<i>beta coefficient</i> <i>(95%CI)**</i>
Any large BMLs			
Absent	186		
Resolved	4	+0.34 (-0.18, +0.90)	+0.34 (-0.20, +0.90)
Incident	4	-0.00 (-0.53, +0.52)	0.00 (-0.52, +0.52)
Persistent	1	+0.60 (+0.41, +0.76)	+0.63 (+0.42, +0.85)
Hip cartilage defects			
Absent	48		
Incident	16	+0.32 (+0.01, 0.62)	+0.36 (+0.03, 0.70)
Persistent	130	-0.00 (-0.20, 0.19)	+0.01 (-0.20, 0.21)
Baseline hip ROA			
Absent	124		
Grade1/Grade 2	41	+0.11 (-0.14, 0.40)	+0.13 (-0.14, 0.40)
Grade3/Grade 4	9	+0.30 (-0.30, 0.85)	+0.42 (-0.15, 0.98)

Independent variable: presence of structural/ radiographic factors. Dependent variable: change in hip effusion- synovitis size

* Adjusted for age, sex and body mass index at phase 2.

** Adjusted for hip cartilage defects or BMLs at phase 2 where appropriate.

Analyses for hip ROA adjusted for both hip BMLs and hip cartilage defects.

Further longitudinal analyses (independent of hip effusion-synovitis) showed that any hip BML predicted incident (PR: 1.62 95%CI: 1.13, 2.34) and worsening hip cartilage defects (PR: 1.50 95%CI: 1.20, 1.86). Conversely, any hip cartilage defect predicted incident (PR: 1.11 95%CI: 1.03, 1.20) and worsening hip BMLs (PR: 1.16 95%CI: 1.04, 1.30).

Discussion

This prospective cohort study describes the correlates of hip effusion- synovitis. Overall there was no association between hip effusion- synovitis and hip pain, however, presence of hip effusion- synovitis at multiple sites (presumably reflecting effusion-synovitis extent) was associated with presence of hip pain. Hip effusion-synovitis did not associate with worsening hip pain. Femoral defects were associated with hip effusion- synovitis CSA both cross-sectionally and longitudinally while any large persistent BMLs predicted an increase in hip effusion- synovitis CSA.

Cross-sectionally, subjects with a hip effusion- synovitis at multiple sites were 42% more likely to have hip pain. Hip effusion- synovitis did not associate with severity of hip pain. Longitudinally, subjects with resolving hip effusion-synovitis showed a decrease in hip pain while subjects with worsening or persistent hip effusion-synovitis had an increase in hip pain. However, these analyses were not statistically significant and adjusting for hip BMLs or hip cartilage defects made no difference. At the hip, three studies besides ours have reported these associations and have found similar inconsistencies. The first study demonstrated that older adults with diagnosed hip OA with hip pain in mid-thigh and pain on palpation had higher odds of major hip effusion-synovitis.¹⁴⁷ While in the second study, a weak association was found between hip pain and grade 1 but not grade 2 synovitis.⁹³ The third and the latest study aiming to validate a hip scoring system found no correlation between hip effusion-synovitis and hip pain score.⁹⁴ These studies lack longitudinal data and measured effusion or synovitis semi-quantitatively. Also, only one of the above studies measured synovitis and effusion separately. While our study has its strengths, we did not assess site-specific hip pain and a cross-sectional association was found only in subjects who had extensive hip effusion- synovitis. We could not differentiate between physiological or pathological joint fluid but overall, it appears that site and extent of effusion- synovitis at the hip may be relevant for pain in OA.

Cross-sectionally, femoral cartilage defects correlated with larger hip effusion-synovitis CSA. Subsequently, incident hip cartilage defects predicted an increase in hip effusion-synovitis size. Persistent hip cartilage defects were not associated with a change in hip effusion-synovitis CSA. An association between incident hip cartilage defects and hip effusion-synovitis has not been previously reported but most of the

existing evidence for knee OA coincides with our findings. For instance, subjects with large knee effusion-synovitis (>grade 2) at baseline had 2.7 times greater risk of knee cartilage damage at the end of 30 months follow-up.¹¹⁵ A recent longitudinal study reported that regional knee effusion-synovitis predicted knee cartilage defects; cartilage volume loss and knee BMLs and these associations were largely mediated by cartilage defects.¹³⁴ Hence, causal pathways exist between knee effusion-synovitis and knee cartilage defects; and suggests that knee cartilage defects could lead to the development of BMLs and cartilage volume loss at the knee joint.¹³⁴ Our results are comparable with these studies and so far, this is the first study to report these associations at the hip.

Hip BMLs associated with hip effusion-synovitis longitudinally. Moreover, this association persisted after adjusting for hip cartilage defects. In knee OA, a positive and modest correlation was reported between knee effusion (but not synovitis) and knee BMLs.²²⁸ A longitudinal study, demonstrated an association between knee effusion-synovitis and knee BMLs but this association was not independent of knee cartilage defects.¹³⁴ We found that persistent large hip BMLs over the period of 2.6 years predicted an increase in hip effusion-synovitis size. Also, hip BMLs were associated with the formation and worsening of hip cartilage defects. These results are consistent with our previous work.¹¹⁴ However, these analyses were based on a limited number of hip BMLs and these results should be interpreted cautiously and further studies are necessary.

Overall, incident hip cartilage defects and persistent large hip BMLs independently predicted an increase in hip effusion-synovitis. Also, hip cartilage defects predicted incident and worsening of hip BMLs and vice-versa. Our data suggests that the association of hip effusion-synovitis could be stronger and more consistent with cartilage defects than BMLs. This could be due to inter-dependency between effusion-synovitis and cartilage. Catabolic and proinflammatory mediators triggered by synovitis lead to intra-articular debris due to cartilage breakdown. In turn, presence of articular debris causes further inflammation of the synovium. Hypothetically, an increase in joint intra-capsular pressure could push synovitis into the subchondral bone through the cartilage defects causing the formation of BMLs.^{116, 134, 139} Moreover, BMLs are known to correlate with not only knee subchondral bone mineral density(BMD)²⁰³ but also with local hip BMD.²²⁹ Thus, suggesting a definite causal

pathway between hip effusion- synovitis, hip defects, hip BMLs and alterations in the bone itself.

High cartilage signal did not associate with hip effusion-synovitis but surprisingly there was no relationship between hip ROA and hip effusion-synovitis either. Here, subjects with grade 3 or 4 hip ROA at baseline had increase in effusion-synovitis CSA at follow-up but these analyses were not statistically significant. An association between hip effusion-synovitis and hip ROA has been described in previous studies. Two cross-sectional studies demonstrated that hip effusion or synovitis associated with greater odds¹⁴⁷ and higher prevalence of hip ROA.⁹³ A third study with 98 subjects reported modest correlations between effusion-synovitis and hip ROA.⁹⁴ These studies measured effusion-synovitis semi-quantitatively. Additionally, the prevalence of severe hip OA (grade>2) in the above studies was between 15%-34% but in our cohort, it was low at 5.4%. We did not separate hip effusion from synovitis and this could affect our results but 2/3 studies above used similar methods. There could be a possibility that hip ROA does not associate with a change in hip effusion-synovitis, in the long run. However, these analyses were conducted in a community-based cohort with a lower severity of disease and further studies are necessary.

Limitations

This was the first study to assess hip effusion-synovitis quantitatively and we have applied similar methods previously^{114, 215} and obtained high reproducibility. The STIR MRI sequence used to examine joint effusion-synovitis did not allow separation of physiological and pathological effusion but our findings allow an assessment of this and match with other MRI-based reports using similar techniques.^{94, 134, 147} Longitudinal analyses were carried out in a small number of subjects with hip BMLs but the results were statistically significant and coincided with existing literature.

Conclusion

Hip effusion- synovitis at multiple sites (presumably reflecting extent) may be associated with hip pain. Hip BMLs and hip cartilage defects are co-dependent and predict worsening hip effusion- synovitis, indicating shared causal pathways between

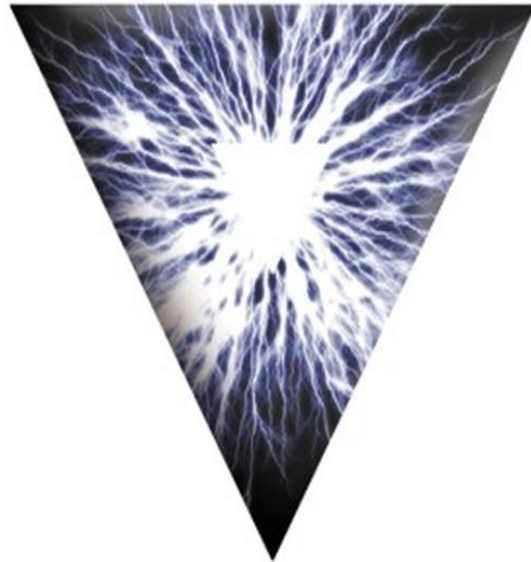
defects, BMLs, and effusion- synovitis. Together, these factors have a deleterious effect on the bone and also contribute towards progression of OA.

Postscript

The aim of this thesis was to determine the associations and understand the pathophysiological changes occurring in the bone in early OA. Structural changes such as BMLs and defects associated with major clinical outcomes such as pain and ROA. Generally, chapters 4-7 demonstrate that in preclinical OA there are shared underlying pathways between effusion-synovitis, cartilage defects, hip BMLs and changes in the bone which may eventually manifest as pain, inflammation, and joint deterioration.

This chapter concludes the studies which focused on describing changes in joint structure and their associations in older adults. The goal of this thesis is not only to study changes in the joint structure but also assess muscle health. Thus, the next chapter includes a mechanist study which uses MRI's to assess hip muscles and then describes their relationship with bone density and leg strength in the TASSOAC cohort.

Chapter 8 : The association between hip muscle cross-sectional area, muscle strength and bone mineral density.



Published in Calcified Tissue International;

2014, 95: 64-72

Harbeer Ahedi, Dawn Aitken, David Scott, Leigh Blizzard,

Flavia Cicuttini and Graeme Jones

(Original article inserted as Appendix VII)

Introduction

Loss of skeletal muscle mass and strength, also known as sarcopenia, has been recognized as a predictor of reduced muscle strength and bone mineral density (BMD),^{156, 230} possibly due common determinants.^{150, 231} Additionally, studies have found that subjects with lower skeletal mass are at higher risk of falls,¹⁵⁷ fractures¹⁵² and loss of function.²³² Muscle cross-sectional area (CSA) is a validated surrogate measure for muscle mass. Research suggests that CSA of the thigh in the elderly predicts hip fractures²³³ and increased risk of osteoporosis.²³⁴ Similarly, individual muscle CSA associates with cartilage,^{159, 235} muscle strength,^{166, 236} joint biomechanics²³⁷ and bone structure.^{151, 238}

In comparison to skeletal mass, fewer studies have investigated the correlations between individual muscle CSA and BMD. For instance, *Revel et.al* compared the associations between psoas, erector spine and triceps brachii muscle CSA and BMD of lumbar spine in 89 post-menopausal women and found a correlation between psoas muscle CSA and spine BMD.¹⁶³ The same group conducted a clinical trial in which 67 post-menopausal women were selected for physical training targeting either the psoas or the deltoid muscles. After 12 months, women who had trained their deltoid muscle had a greater loss in spine BMD in comparison to women who had trained their psoas muscle [-8.87% v +0.14%].²³⁹ These studies suggest that local muscles, which insert directly into the bone, are involved in the preservation of bone density. Furthermore, in a magnetic resonance imaging (MRI)-based cross-sectional study, *Klein et.al* suggested that both upper arm muscle CSA and forearm muscle CSA were the best predictors of humerus and forearm cortical bone health.²³⁸ Lastly, in a longitudinal study using peripheral quantitative computed tomography (pQCT), *Edwards et.al* found larger forearm CSA was positively associated with higher radial bone mineral content and bone area but not bone density.¹⁵¹ These studies support the Wolf and Frost theory,^{65, 66} which proposes, that the increase in bone mass is due to muscle accumulation on bone and muscle recruitment and contraction during locomotion.

Skeletal muscle is not only linked with bone mass but also influences variability in strength.^{237, 240} Although muscles have been examined as groups; studies investigating

the relationship between individual muscles and strength are rare. *Masuda et.al* investigated the correlation of isokinetic muscle strength and muscle CSA of the lower limb in 14 healthy soccer players (age 19-22 yrs.) and reported that CSA of gluteus medius and minimus (scored together) and gluteus maximus were strongly correlated with hip abductor strength. Additionally iliopsoas muscle CSA was moderately correlated with hip flexion strength.¹⁶⁶ *Takai et.al*, conducted a cross-sectional study in older adults (age 63-64 yrs.) and found a very strong correlation between quadriceps muscle CSA and isometric knee extension force during sit-to-stand testing.¹⁶⁷ Furthermore, *Frontera et.al* investigated the longitudinal changes in muscle CSA and muscle strength in 9 men (age 65yrs.) for 12 years and concluded that variation in muscle CSA was accountable for 90% of variability in muscle strength.

In general, association between muscle mass and measured individually or as a group is positively associated with BMD and strength. However, firstly, less is known about the relationship of individual muscles and bone mass. Furthermore, studies suggest that muscles having a direct link with the joint and those which are recruited often, might have a greater influence on bone mass. Secondly, examining the relationship between muscle CSA and muscle strength provides greater understanding of muscle morphology and also aids in maintaining muscle strength in older adults. Thus, the objective of our study was to describe the cross-sectional associations between individual hip muscles, muscle strength and bone density at the hip, femoral neck and spine.

Methods and Materials

TASOAC cohort

This study was conducted as a part of the Tasmanian Older Adult Cohort (TASOAC) study, a prospective, population-based study initiated in 2002 aimed at identifying the environmental, genetic and biochemical factors associated with the development and progression of OA at multiple sites (hand, knee, hip and spine). Subjects between the ages of 50 to 80 years were randomly selected from the electoral roll of Southern

Tasmania (population 229,000), with an equal number of men and women. The overall response rate was 57%. As TASOAC was designed to examine community-dwelling older adults and hence all institutionalized older adults were excluded. Participants were also excluded if they had a contraindication for MRI, including previous hip replacements. Of all initially eligible participants, 1,100 enrolled in the study, and 1,099 attended a baseline (Phase 1) clinic between March 2002 and September 2004. Follow-up data (Phase 2) was collected for 875 participants at a clinic approximately three years later and then again for 769 participants (Phase 3) at a clinic approximately five years later.

Hip MRI scans were added to the study in the later stages of phase 2. 328 subjects had a right hip MRI (T1-weighted) at phase 2 and of these 7 subjects had missing data or corrupted MRIs leaving 321 with complete data. No subject included in this study had a history of hip fracture at phase 2. In addition, at baseline (Phase 1) subjects included in the current study ($n=321$) were younger (age: 61.6 v 63.6, $p<0.001$) in comparison to the rest of the TASOAC cohort ($n=778$), however no other differences in sex, BMI, bone mineral density and leg strength were found between the two populations. Written informed consent was obtained from all participants and the Southern Tasmanian Health and Medical Human Research Ethics Committee approved this study.

Clinical measurements

Demographic characteristics, medical history, and lifestyle factors were assessed by self-administered questionnaires. Height was measured to the nearest 0.1 cm using a stadiometer (with shoes, socks and bulky clothes removed). Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothes removed) using a single pair of electronic scales (Seca Delta model 707; Hamburg, Germany). Body mass index (BMI) was calculated as the weight (kg) divided by height (m^2).

Magnetic Resonance imaging

An MRI scan of the right hip was performed. The hip was imaged in the sagittal plane using a 1.5 Tesla G.E signal whole-body magnetic resonance unit with a phased-array flex coil. The following image sequence was used: a T1-weighted fat-suppressed 3-dimensional gradient-recalled acquisition in the steady state; flip angle 55°; repetition time 58 msec; echo time 12 msec; field of view 16 cm; 60 partitions; 512 x 512-pixel matrix; acquisition time 11 minutes 56 seconds, and 1 acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.39 x 0.39 mm (512 x 512 pixels). In this study the approximate range of hip MRI images was from the middle of greater sciatic notch in the pelvis to the end of the lesser trochanter of the femur.

Measurement of muscle cross-sectional area (CSA)

Hip muscles were identified and chosen for measurement as per MRI field of view (figure 3-3). Measurements of clearly visible muscle CSA, where the entire area of the muscle was visible and distinguishable from the adjacent muscles were made at the anatomical landmarks described in Table 8-1. Hip muscle area was assessed on MR images using OsiriX (Geneva) software measuring maximum muscle CSA (cm²) of gluteus maximus, obturator externus, gemelli, quadratus femoris, piriformis, pectineus, sartorius and iliopsoas (Figure 8-1). If any of the hip muscles above were not distinguishable from adjacent muscles they were not measured; hence not all eight muscles were measured in all subjects. The CSA of each hip muscle was measured on two consecutive slices by one trained observer (HA) and the average was taken as the final measurement. The majority of hip muscles were measured on sagittal MR images except iliopsoas, which was measured by reformatting the whole sagittal image to the axial plane. The superior and inferior gemelli were measured together. The intra-class correlation coefficient (ICC) for the retest-reliability after two weeks (n=40, same observer) was calculated for each muscle using the ICC (3,1) formula. The ICCs for all hip muscle CSAs ranged from 0.98-0.99.

Anatomical landmarks of hip muscle CSA

Table 8-1: Hip muscles anatomical landmark chart.

Hip Muscle	Anatomical Landmark
Hip extensor	
Gluteus Maximus	First appearance of the femoral head cartilage in sagittal section
Hip rotators	
Obturator externus	First appearance of the femoral head cartilage in sagittal section
Gemelli	First appearance of the femoral neck.
Quadratus femoris	Round head of the femur is no longer visible in the sagittal section
Piriformis	First appearance of the bony femoral head in sagittal section
Hip flexors	
Pectineus	First appearance of the femoral head cartilage in sagittal section (adjacent to obturator externus)
Iliopsoas	Total visibility of the femoral fovea in axial section
Sartorius	First appearance of the femoral neck in sagittal section

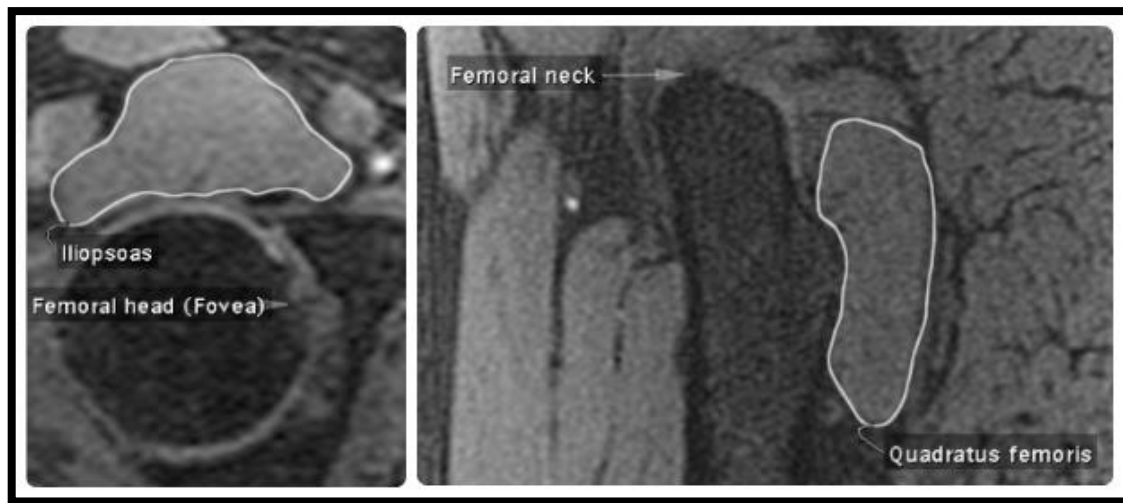


Figure 8-1: Measurement of hip muscle CSA using OsiriX imaging software.

(Iliopsoas and quadratus femoris CSA shown as examples)

Bone mineral density

Bone density (g/cm^2) was assessed using dual-energy X-ray absorptiometry (DXA) at the right total hip, femoral neck and spine using a single Hologic Delphi densitometer (Waltham, MA, USA). The longitudinal coefficient of variation for our densitometer using a spine phantom was 0.39%. [241](#)

Muscle strength

Leg strength (Figure 8-2) was measured to the nearest kilograms in both legs simultaneously, using a dynamometer (TTM Muscular Metre, Tokyo, Japan). This test examines isometric strength, predominantly of the quadriceps and hip extensors, and has been described in detail previously. [218](#)



Figure 8-2: Demonstration of the leg strength measurement in TASOAC

Physical activity

Physical activity was assessed as steps/day determined by (Yamax SW-200, Yamax USA, San Antonio, Texas, USA). Each participant was instructed to wear the pedometer for seven consecutive days. This was repeated 6 months later for seasonal variations. Mean steps/day was calculated as the average of the days worn at both time points.

Statistical analyses

The characteristics of the subjects are summarized as means and standard deviations (SD), and for men and women separately because of the sex-related differences in muscle CSA. Associations between bone mineral density at the hip; femoral neck, and spine and muscle CSA are summarized as standardized regression coefficients. In order to test whether the association between muscle and spine BMD was independent to local BMD, the analysis for spine BMD was adjusted for hip BMD. The associations of hip and femoral neck BMD with pectineus and sartorius CSA varied by sex as determined by tests of statistical interaction, and are presented for men and

women separately. Regression analyses were also conducted with muscle strength as the response variable, and in this case the results of association with iliopsoas are presented for men and women separately, based on significant interaction. Lastly, regression models were used to examine the association between muscle strength and bone density. All statistical models were adjusted for age, sex (where appropriate) and steps per day but not body size as muscle size was a key focus of this study. All statistical tests were two sided and p values < 0.05 were considered significant. All statistical analysis was conducted using Intercooled Stata 12 for Mac (Stata Corp. College station, TX, USA)

Results

Characteristics of the study sample

Table 8-2 describes the characteristics of the study sample. There was similar mean age and mean BMI in men and women, however, men had higher mean muscle strength, muscle CSA, steps per day and bone mineral density of hip, femoral neck and spine.

Table 8-2: Characteristics of the subjects

Characteristics	Men (n=167)	Women (n=158)
Age (yrs.)	64.04 (7.47)	63.26 (6.60)
BMI (kg/m ²)	27.50 (3.91)	28.13 (5.23)
Total hip BMD (g/cm ²)	1.02 (0.13)	0.90 (0.13)
Femoral neck BMD (g/cm ²)	0.80 (0.11)	0.74 (0.11)
Spine BMD (g/cm ²)	1.07 (0.17)	0.96 (0.15)
Leg strength (kg)	135.32 (45.7)	63.11 (28.9)
Steps per day	8268 (3703)	7384 (3234)
Gluteus Maximus CSA (cm ²)	51.40 (13.6)	42.20 (8.05)
Obturator Externus CSA (cm ²)	9.31 (1.83)	7.11(1.13)
Gemelli CSA (cm ²)	4.33 (1.00)	3.50 (0.93)
Quadratus femoris CSA (cm ²)	7.20 (2.46)	5.92 (1.70)
Pectineus CSA (cm ²)	10.31 (2.09)	7.71 (1.84)
Piriformis CSA (cm ²)	4.92 (1.52)	3.87 (1.24)
Sartorius CSA (cm ²)	10.24 (3.67)	7.71 (2.24)
Iliopsoas CSA (cm ²)	10.08 (1.81)	7.63 (1.48)

Data presented as means (sd).

CSA= cross-sectional area.

BMD = bone mineral density.

Bone density and hip muscle CSA

Table 8-3 shows the associations between bone density and muscle CSA as standardized regression coefficients. Apart from pectineus and sartorius, data for males and females are combined, as there was no interaction. For pectineus and sartorius CSA, the associations with bone density were stronger for women than for men.

Both obturator externus and quadratus femoris CSA were positively associated with hip and, to a lesser extent, femoral neck BMD, but CSA of piriformis and gluteus maximus showed no association with BMD at any site. The associations of all hip flexors with bone density of hip and femoral neck were similar and statistically significant. Lastly, of all the hip muscles, only gemelli CSA was associated with spine BMD.

Table 8-3: Cross-sectional relationship between hip muscle CSA and bone density at the hip, neck and spine

Study factor	N	Total hip BMD (g/cm ²)	Femoral neck BMD (g/cm ²)	Spine BMD (g/cm ²)
		Standardized β (95 % CI) (Adjusted) [†]	Standardized β (95 % CI) (Adjusted) [†]	Standardized β (95 % CI) (Adjusted) [†]
Hip extensor				
Gluteus maximus (cm ²)	84	0.01 (-0.28, 0.31)	-0.00 (-0.35, 0.27)	-0.03 (-0.19, 0.13)
Hip rotators				
Obturator Externus (cm ²)	219	0.18 (0.00, 0.35)	0.26 (0.10, 0.40)	0.05 (-0.07, 0.16)
Gemelli (cm ²)	130	0.04 (-0.12, 0.21)	0.03 (-0.14, 0.20)	0.20 (0.08, 0.33)
Quadratus femoris (cm ²)	236	0.19 (0.07, 0.31)	0.16 (0.03, 0.30)	0.04 (-0.06, 0.14)
Piriformis (cm ²)	240	0.11 (-0.02, 0.23)	0.06 (-0.06, 0.20)	0.07 (-0.02, 0.17)
Hip flexors				
Pectineus (cm ²)	153	0.22 (0.06, 0.37)	0.21 (0.05, 0.36)	0.09 (-0.06, 0.23)
Men	87	0.18 (-0.05, 0.42)	0.14 (-0.10, 0.37)	-
Women	66	0.27 (0.05, 0.56)	0.31 (0.09, 0.52)	-
Interaction (p value)		<i>p=0.04</i>	<i>p=0.01</i>	
Sartorius (cm ²)	145	0.22 (0.06, 0.37)	0.26 (0.09, 0.42)	0.05 (-0.06, 0.17)
Men	55	0.13 (-0.15, 0.41)	0.09 (-0.19, 0.37)	-
Women	90	0.29 (0.09, 0.48)	0.41 (0.23, 0.59)	-
Interaction (p value)		<i>p=0.06</i>	<i>p=0.001</i>	
Iliopsoas (cm ²)	215	0.20 (0.05, 0.36)	0.20 (0.03, 0.35)	0.03 (-0.08, 0.15)

Bold face indicates statistically significant. Independent variable: hip muscles. Dependent variable: BMD at hip, neck and spine.

[†] Adjusted for age, sex and steps per day. Additionally, models for spine BMD have been adjusted for hip BMD

β coefficient (standardized) represents cross-sectional increase in bone density at hip, neck and spine BMD with per unit increase in CSA of hip muscles.

Hip muscle CSA and muscle strength

Table 8-4 presents the associations between hip muscles CSA and muscle strength. All hip muscles except gemelli and gluteus maximus were positively but weakly associated with muscle strength.

Table 8-4: Cross-sectional associations between hip muscle CSA and muscle strength.

Study factor	N	Standardized β (95 % CI) (Adjusted) [†]
Hip extensor		
Gluteus maximus (cm ²)	81	0.11 (-0.01, 0.23)
Hip rotators		
Obturator externus (cm ²)	206	0.16 (0.05, 0.28)
Gemelli (cm ²)	125	0.08 (-0.06, 0.21)
Quadratus femoris (cm ²)	222	0.14 (0.04, 0.24)
Piriformis (cm ²)	226	0.12 (0.02, 0.23)
Hip flexors		
Pectineus (cm ²)	144	0.16 (0.04, 0.28)
Sartorius (cm ²)	135	0.12 (0.01, 0.23)
Iliopsoas (cm ²)	205	0.24 (0.12, 0.37)
Men	95	0.32 (0.15, 0.49)
Women	110	0.17 (0.01, 0.35)
<i>Interaction (p value)</i>		<i>p=0.02</i>

Bold face indicates statistically significant

Independent variable: hip muscles. Dependent variable: leg strength.

n= number of observations.

[†] Adjusted for age, sex and steps per day.

β coefficient (standardized) represents cross-sectional increase in leg strength with per unit increase in CSA of hip muscles.

Lastly, hip BMD was associated with muscle strength (β : 0.12 95%CI 0.04, 0.20).

Additionally, spine BMD showed a weak association with muscle strength (β : 0.10

95%CI: 0.00, 0.21) and the association between femoral neck BMD and muscle strength (β : 0.07 95%CI: -0.00, 0.15) did not reach statistical significance.

Discussion

This is the first population-based study describing the associations between hip muscles CSA, muscle strength and bone density. In the present study, all hip flexor CSAs were associated with bone density and of these, associations for pectineus and sartorius were stronger for women in comparison to men. Among the hip rotators, obturator externus and quadratus femoris was associated with hip and femoral neck BMD. Gemelli was the only hip muscle that associated with spine BMD. Lastly, most of the hip muscles were associated with muscle strength and overall, muscle strength was weakly correlated with BMD.

In general, all hip muscles were positively associated with bone density of the hip, femoral neck and spine. We adjusted for age and sex but not for body size. We acknowledge that this could lead to bias but we believe that as both, muscle size and BMD correlate with body size, any adjustment for body size would be an over adjustment. For instance, when we adjusted for BMI in the analyses between total hip BMD and muscle CSA, we noted a 2% to 63% reduction in the standardized regression coefficients (average of 44% change). This change occurs because of the strong correlation between muscle CSA and BMI. Thus, the issue with adjustment for BMI or any mass related factor is that it may also reduce any genuine association between muscle size and BMD.

Most of the hip muscles, especially hip flexors, were associated with hip and femoral neck BMD but these associations differed in men and women. Of the hip rotators, quadratus femoris and obturator externus showed a weak association with BMD of hip and femoral neck but no difference by gender was found. The reasons for this are unclear. The literature on the relationship between skeletal muscle mass and bone density in men and women is controversial.^{[151](#), [152](#), [231](#), [242-244](#)} The available data does not allow clear conclusions due to differences in methodology, subjects and study

designs. One possible explanation is that there are higher flexion and greater hip contact forces in women in comparison to men.²⁴⁵⁻²⁴⁷ Thus it could be speculated that due to higher flexion and greater hip contact forces the relationship between bone density and hip flexion is stronger in females, however we did not measure biomechanical factors in this study.

Unexpectedly, some muscles did not show any associations with bone density or strength. For instance, no association was found between gluteus maximus size, muscle strength and bone density. This muscle is known to associate with muscle strength ¹⁶⁶ but its association with bone density is currently unknown. These irregularities could be explained by our inability to assess the maximal muscle bulk due to limited MRI field of view (especially for the gluteus maximus muscle although it should be noted that the measured CSA was greater than any of the other measured muscle). An alternative potential explanation as to why gluteus maximus CSA was not associated with muscle strength is that other hip extensor muscles, which were not assessed in this study, may have been recruited preferentially to this muscle during the strength assessment.

Studies show that piriformis is activated during exercise and is mainly involved in hip rotation and does contribute to hip strength and stability.²⁴⁸ In the present study, piriformis was weakly associated with muscle strength but not with bone density. Our findings support this fact, however like, gluteus maximus, the relationship of piriformis with bone density is unknown and nor does it associate with hip cartilage volume in subjects with or without hip OA.²³⁵ Thus, evidence suggests that preservation of piriformis may result in better hip stability and perhaps this muscle has no role in maintenance of bone mass.

Skeletal muscle mass has been found to be associated with hip and spine BMD²³¹, however in this study the correlations between hip muscle CSA and BMD were mostly local (i.e hip and femoral neck) with the exception of gemelli, which was associated with spine BMD. Gemelli, is a deep hip rotator and has been proposed to play a vital role in hip/pelvic stability.²⁴⁹ For instance, when hip rotators were spared during surgery, hip dislocation and function deficit rates dropped dramatically¹⁴⁹ and one study reports that gemelli CSA was positively associated with hip cartilage

volume in subjects without hip OA ($p=0.02$).²³⁵ Thus, gemelli may play a role in osteoarthritis disease progression however its association with spine BMD is unclear. Nevertheless, it has been suggested that gemelli may fuse with its neighboring muscle, obturator internus and mimic its functions.²⁵⁰ Obturator internus plays a vital role in stabilization of the pelvis, which is interdependent on the spine for its stability. Thus, we could speculate that due to its association with obturator internus, gemelli might show an association with spine BMD. Again, this is purely hypothesis generating and future studies need to explore this concept further.

The mechanostat theory of Wolf suggests that muscles have a direct impact on bone and muscle contraction and/or stress on the bone, stimulates an increase in bone mass.^{65, 66, 251} Our findings are in accord with this theory and demonstrate that increasing hip muscle size was positively associated with increased local bone density and muscle strength. A few studies support our findings and suggest that muscle CSA and strength could predict changes in bone health and perhaps bone density,^{151, 238} although some variations do exist. In studies by *Edwards* and *Klein et.al*, the association of bone parameters, muscle strength and muscle CSA of the arm and forearm was investigated. Consistent with our results, both studies reported that muscles CSA (forearm and arm) but not muscle strength was a better predictor of bone measures. However, one of the studies measured radial cortical bone area using MRI²³⁸ and the other study used pQCT for assessing bone.¹⁵¹ In the second study, an association between muscle CSA, bone area, bone mineral content and bone strength but not bone density was found¹⁵¹. In comparison to these, we found lower but significant associations between hip muscles and bone density. This may suggest that assessment of actual bone area or bone structure by MRI or pQCT could be more sensitive than bone density measured by DXA or that relationships alter with increasing age.²⁵²

The relationship between muscle strength and muscle CSA has been investigated^{151, 236, 237, 253} and both of these factors are affected by age²³⁸ and disease.^{161, 236} Our data is consistent with current literature and expands it showing moderate, consistent associations between hip muscles and muscle strength in older adults (albeit the associations were weaker as compared to other studies). Additionally, not all hip muscles showed an association with strength. Our study includes community-based

older adults who were unlikely to be involved in vigorous activity, which may influence this association. Furthermore, we used only one parameter for assessing muscle strength that is mostly applied for measuring hip extensor strength and hence may not equate with other strength measures used in other studies.^{166, 167} For instance, *Takai et.al* reported a strong correlation between quadriceps CSA and knee extension force that was measured by myometer.¹⁶⁷

It is evident that decline in muscle mass has a significant impact on bone mass and strength.^{156, 231} Even though muscle morphology has been explored in biomechanical studies^{164, 168} it has gain less attention in osteoporosis and/or osteoarthritis (OA). In addition, unlike bone, muscles have some capacity to regenerate.^{64, 254} Hence MRI studies, like ours, looking into individual muscles can be used for better understanding of changes in muscle morphology in older adults, who are more vulnerable to the development of OA or osteoporosis. Such studies could aid in targeted rehabilitation, which can be applied for management of disease progression and maintenance of bone mass.

Limitations

This is a cross-sectional study, thus we are unable to determine causal pathways but our results were consistent with the existing data. Bone density was measured using DXA, which provides an aerial two-dimensional BMD measure that can be influenced by differences in bone size. However, we adjusted for age and sex, which are reasonable surrogates of bone size differences but did not adjust for other body size related covariates for the reasons outlined above. In addition, the comparison of unilaterally measured BMD and muscle CSA with bilaterally assessed leg strength might have influenced our findings. We measured isometric strength and the associations may differ with alternate strength measures. In this study we were unable to exclude muscle infiltrates and also could not capture the maximal muscle bulk of some muscles due to limited MRI field of view. Furthermore, some muscles were not visible on the MRI scans thus we were unable to assess all hip muscles in each participant or adjust for independent effects of each muscle.

Conclusions

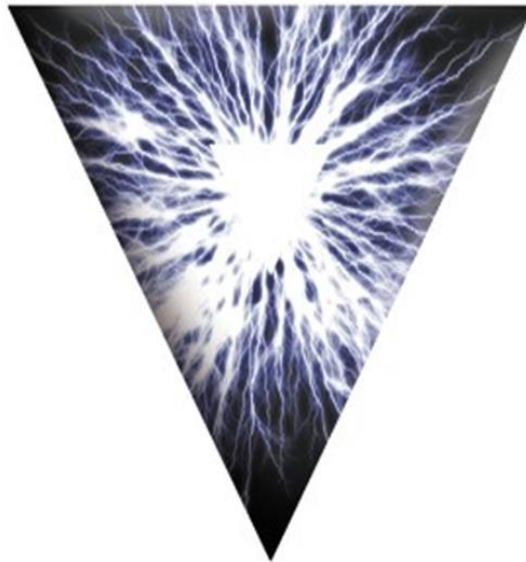
Overall, hip muscle CSA (especially the hip flexors), and to a lesser extent, muscle strength were positively associated with hip BMD. This data suggests that both higher muscle mass and strength may contribute to the maintenance of bone mass and prevention of disease progress in the older adult.

Postscript

CSA is a well-known surrogate measure for muscle mass and this study uses this measure to describe the link between muscle mass, muscle strength, and bone density.

The study outlined in the next chapter uses DEXA images from phase 1 of the TASOAC cohort and ASM (software) to assess the global shape of the proximal femoral head. Furthermore, it aims to describe the importance of variations in shape of the hip bone and how it could relate to factors associated with progression of hip OA. This is the only study in which TASOAC phase 4 data has been used and this study were conducted in collaboration with the University of Aberdeen, U.K.

Chapter 9 : Hip shape as the predictor of osteoarthritis progression in a prospective population cohort.



This chapter is under peer review in Arthritis Care and Research
Harbeer Ahedi, Richard. Aspden, Leigh Blizzard, Fiona. Saunders, Flavia Cicuttini,
Dawn Aitken, Graeme Jones and
Jennifer Gregory.

Introduction

Osteoarthritis (OA) is a musculoskeletal disorder that affects the elderly population around the globe and imposes a considerable economic burden on society.¹⁰ Though OA is a disease of the whole joint, bone and cartilage still remain the focus of its clinical manifestation.¹⁷ Structural changes such as bone marrow lesions (BMLs) and cartilage defects may have a link with progression of hip OA.^{135, 136, 215, 229} In addition to these, morphology of the hip may also predict development of hip OA,¹⁷⁰ but most current assessments are semi-quantitative and focus on changes in the cartilage and the presence of bony outgrowths.^{171, 172} However, subtle morphological changes are difficult to detect by predefined geometrical measures and do not capture the total morphology of the hip.

Statistical shape modelling (SSM)²⁵⁵ is a sophisticated technique that yields a quantitative measure of hip morphology from two-dimensional images of the joint, such as radiographs,¹⁷⁰ and can identify subtle shape variation within a population. An SSM generates a set of linearly independent '*modes of variation*', each of which describes a coordinated pattern of variation in hip shape within a study group. Each mode has a mean of zero and unit standard deviation. Every image is then assigned a score for each mode describing how many standard deviations it lies from the mean. For instance, in a longitudinal study using radiographs from the Rotterdam study, subjects who had low scores for mode 6 (describing the upper femoral neck with a sharper transition from the femoral head into the lower femoral neck) at baseline were at higher risk of developing severe hip OA and total hip replacement (THR).¹⁷⁰ Subsequently we have shown that SSM can be used to model DXA (dual-energy x-ray absorptiometry) images²⁵⁶⁻²⁵⁸ and that Kellgren-Lawrence (K-L) grading can be applied to these images with as much precision as to radiographs.²⁵⁸ In another longitudinal, nested, case-controlled study of elderly women, hip shape modes specifically reflecting sizes of the femoral head, femoral neck or greater trochanter modestly predicted hip OA.¹⁸² Moreover, hip shape modes could also predict THR independently of clinical, geometrical and radiological factors.²⁵⁹ However, shape modes describing radiographic OA (ROA) may not necessarily associate with clinical descriptors such as pain or crepitus.^{183, 184} Hence, different shape modes might be

better at predicting either clinical or radiological progression of hip OA and may differ between males and females as they have different hip and pelvic shapes.²⁶⁰

OA is a multifactorial disease and it is unknown to what extent morphological aspects of the hip relate to disease progression. Studies to date have shown that SSM is a powerful quantitative tool and is sensitive to changes in bone shape,^{170, 175, 182, 183, 259, 261} but it has not been used to study hip OA in a large community-based cohort and has not previously been tested for associations with BMLs or effusion-synovitis. Thus, the aim of this study was to describe the association between hip shape measured at baseline and clinical, demographical, structural and radiological features of hip OA both at baseline and over time in an older adult Australian cohort using a combination of radiographic, MRI, DXA and patient questionnaire data.

Materials and Methods

Subjects

The Tasmanian Older Adult Cohort (TASOAC) study is an ongoing prospective, population-based study initiated in 2002. A total of 1,100 subjects were enrolled in the study between March 2002 and September 2004 (phase 1). Follow-up data for three clinic visits (phase 2, 3 and 4) were collected for 875, 769 and 531 participants respectively. These visits were conducted approximately 3 years, 5 years and 10 years from baseline (phase 1).

A total of 1099 subjects attended a clinic for baseline measurements (phase 1). Of these, 264 subjects did not have a DXA image and images for 4 subjects were corrupted, leaving 831 subjects with complete baseline data. Hip joint shape was measured from baseline DXA scans. All other measures were collected from clinical visits or questionnaires between baseline and the 5 year (phase 3) follow-up apart from THR which was recorded up to 10 years (phase 4) (Figure 9-1). Written informed consent was obtained from all participants and the Southern Tasmanian Health and Medical Human Research Ethics Committee approved this study.

At baseline and all follow-up assessments demographic characteristics, medical history and lifestyle factors were assessed by self-administered questionnaires. Height

and weight were measured and body mass index (BMI) calculated using standard protocols.⁸⁶ At each follow-up assessment, participants were asked if they had undergone total hip replacement surgery and in which hip.

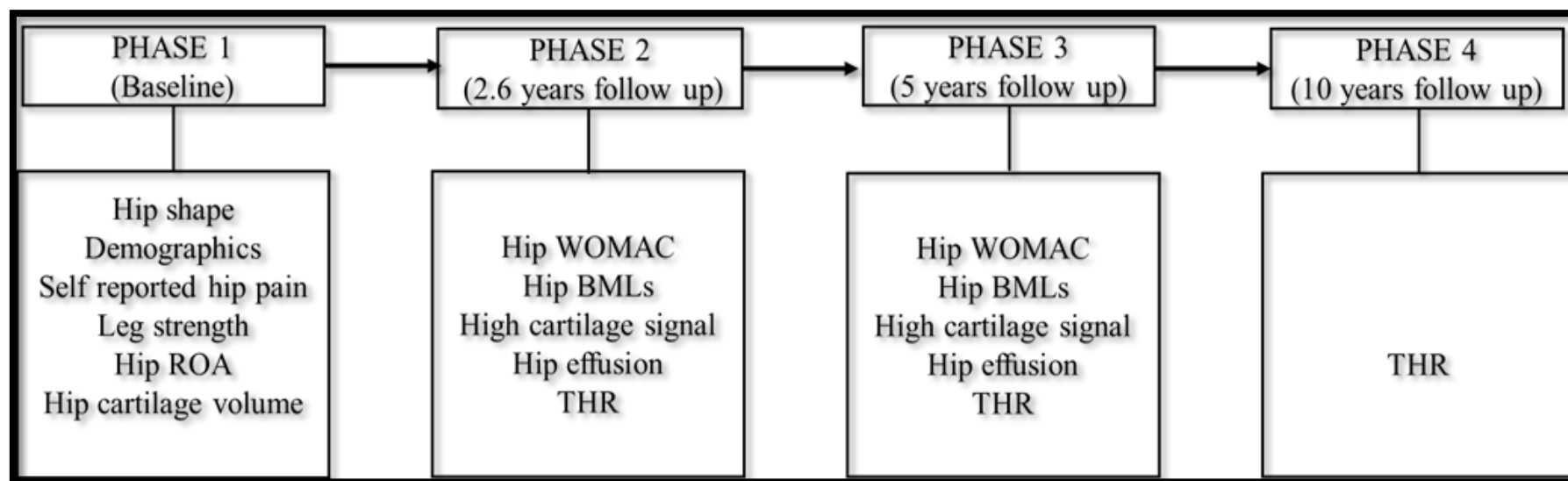


Figure 9-1 Flow chart presenting the measures used in the current study at each time point.

Pain

At baseline, self-reported hip pain was recorded as yes/no using a standardized questionnaire. The presence and severity of hip pain for all the subjects at the follow-up visits for phases 2 and 3 were determined using a hip-specific Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index pain score⁸⁹.

Muscle strength

Muscle strength (leg strength) was measured at each visit to the nearest kilogram-force in both legs simultaneously, using a dynamometer (TTM Muscular Metre, Tokyo, Japan) as described previously.²¹⁸

Magnetic resonance imaging (MRI)

The right hip was imaged in the sagittal plane using a 1.5 Tesla GE Signa whole-body magnetic resonance scanner with a phased-array flex coil using two sequences.

Sagittal images were obtained at a partition thickness of 1.5 mm with an in-plane resolution of 0.39 x 0.39 mm (512 x 512 pixels)⁸¹ using, a T1-weighted, fat-suppressed, 3-dimensional gradient-recalled acquisition in the steady state. The parameters for this were: flip angle 55 degrees; repetition time 58 ms; echo time 12 ms; inversion time (IT) 130 ms; field of view 16 cm; 60 partitions; 512 x 512-pixel matrix; acquisition time 11 mins 56 s, and one acquisition.

A second set of sagittal images was obtained with a slice thickness of 3.5 mm and an inter-slice gap of 1.5 mm²¹⁵ using a STIR-weighted, fat saturation two-dimensional fast spin echo sequence. This sequence used a repetition time 4340 ms, echo time 28.4 ms; field of view 20 cm; 15 partitions (16 slices) and 512 x 512-pixel matrix.

Hip cartilage volume

Baseline femoral head cartilage volume was measured for each individual from the T1-weighted images by one reader at an independent workstation using the software program Osiris (Windows version 3.5; Geneva University Hospital, Geneva,

Switzerland). The volume of the femoral head cartilage was calculated by manually drawing contours around the cartilage boundaries on each image section. These data were then resampled by bilinear and cubic interpolation for the final 3D rendering. Intra-observer reliability was assessed and the coefficient of variation (CV) was 2.5%.^{[81](#)}

Hip bone marrow lesions (BMLs)

Quantitative assessment of subchondral hip BMLs was done using OsiriX software (University of Geneva, Geneva, Switzerland). BMLs were identified as areas of increased signal intensity adjacent to the subchondral bone on the femoral head and/or the acetabulum.^{[215](#), [229](#)}

High cartilage signal

High cartilage signal intensity was identified as an increase in the signal intensity of the articular cartilage due to increased water content that appears as a bright band in the cartilage^{[122](#), [128](#)} either adjacent to a hip BML or at any location on the STIR MRI slice if there was no BML present. High cartilage signal was graded as 0 for absent and 1 for present.^{[215](#), [229](#)}

Hip effusion-synovitis

Hip effusion-synovitis was identified and assessed in STIR images from phase 2 and phase 3. The observer (HA) manually selected the MR slice with the largest effusion-synovitis and determined the maximum cross-sectional area (CSA) of the bright region by manually drawing contours around the outer edges. In a reliability study of 40 subjects with re-measurements after four weeks, the intra-rater agreement (kappa) for presence of hip effusion-synovitis was 0.84, and the ICC (3, 1) for hip effusion-synovitis CSA was 0.97.

Radiological assessment

Antero-posterior radiographs of the pelvis were obtained with the individual weight-bearing and with both feet in 10 degrees' internal rotation. Radiographic features of joint space narrowing (JSN) (axial and superior) and osteophytes (superior acetabular and femoral) of both hips were graded separately on a 4-point scale, ranging from 0 to 3 where 0= no disease and 3= most severe disease. The total radiographic OA score was calculated by summing the JSN and osteophyte scores.⁸⁶ A non-zero score of either JSN or osteophytes was regarded as evidence of hip ROA. Thus, after combining JSN and osteophytes score, the presence of hip ROA was defined as a total score of 1 or greater. For the purpose of this study data for left hip ROA was used.

DXA imaging and Statistical shape modelling (SSM)

At phase 1, DXA images were taken of the left hip using a Hologic Delphi scanner. Images were extracted from the Hologic data files using custom-made Matlab software (Math Works Inc, Natick, United States) and saved as 8-bit BMP files.

An 85-point SSM was built to assess the shape of the femoral head, acetabulum and femoral neck using the Active Shape Modelling toolkit (University of Manchester, Manchester, UK). This model included not only the femoral head shape but also osteophytes, the acetabulum and cortical thickness. The SSM template is a set of landmark points that define the shape to be identified. For comparison between images, each point is always placed on the same anatomical feature on the outline of the bone (Figure 9-2).

The coordinates of the points were collected and transferred to custom-written SHAPE software (University of Aberdeen, UK). Using SHAPE, the data underwent Procrustes transformation, to remove size and orientation effects, and were subjected to principal components analysis to generate an independent set of orthogonal mode scores for each image.¹⁸³ The distribution of each mode is normalized to zero mean and unit standard deviation so that the scores assigned to each image are in units of standard deviations. Reference to a '*lower*' score, therefore, implies a position towards the more negative end of the distribution rather than smaller in absolute

terms. A scree plot was generated to visualize the variance described by each mode and the first 6 shape modes (figure 9-3) were selected; all explained more than 3.5% of the total variance.

A set of 10 images were selected at random from the dataset and the points placed on the images by two independent observers (HA & FRS). Point-to-point variability between observers (the distance between a point's coordinates when placed by each observer) was assessed using custom code in Matlab and the median was 1.6 pixels. Testing for normality using the Shapiro-Wilk test showed a non-normal distribution so the median was used rather than the mean.^{[179](#)}

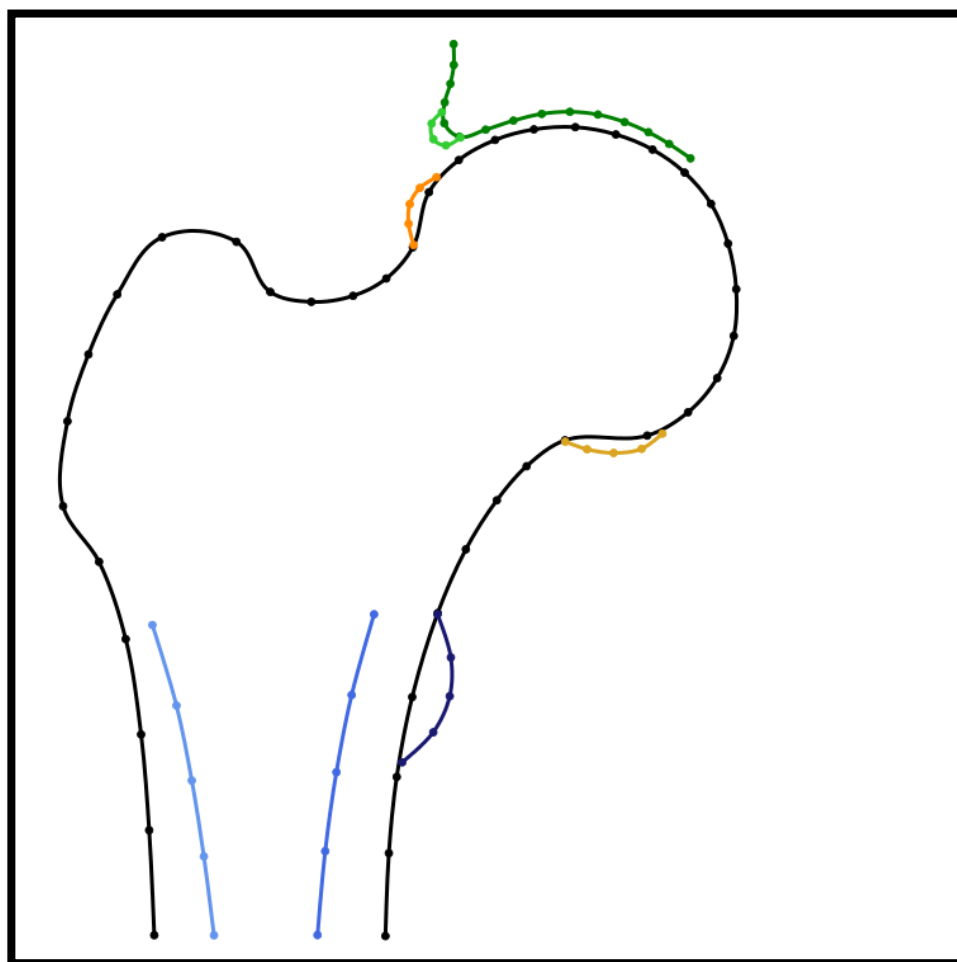


Figure 9-2: 85-point hip model describing the proximal femur, acetabulum and osteophytes

(Where no osteophytes are present, points are mapped onto the neighbouring bone surface). Each line of the template is shown in a different colour.

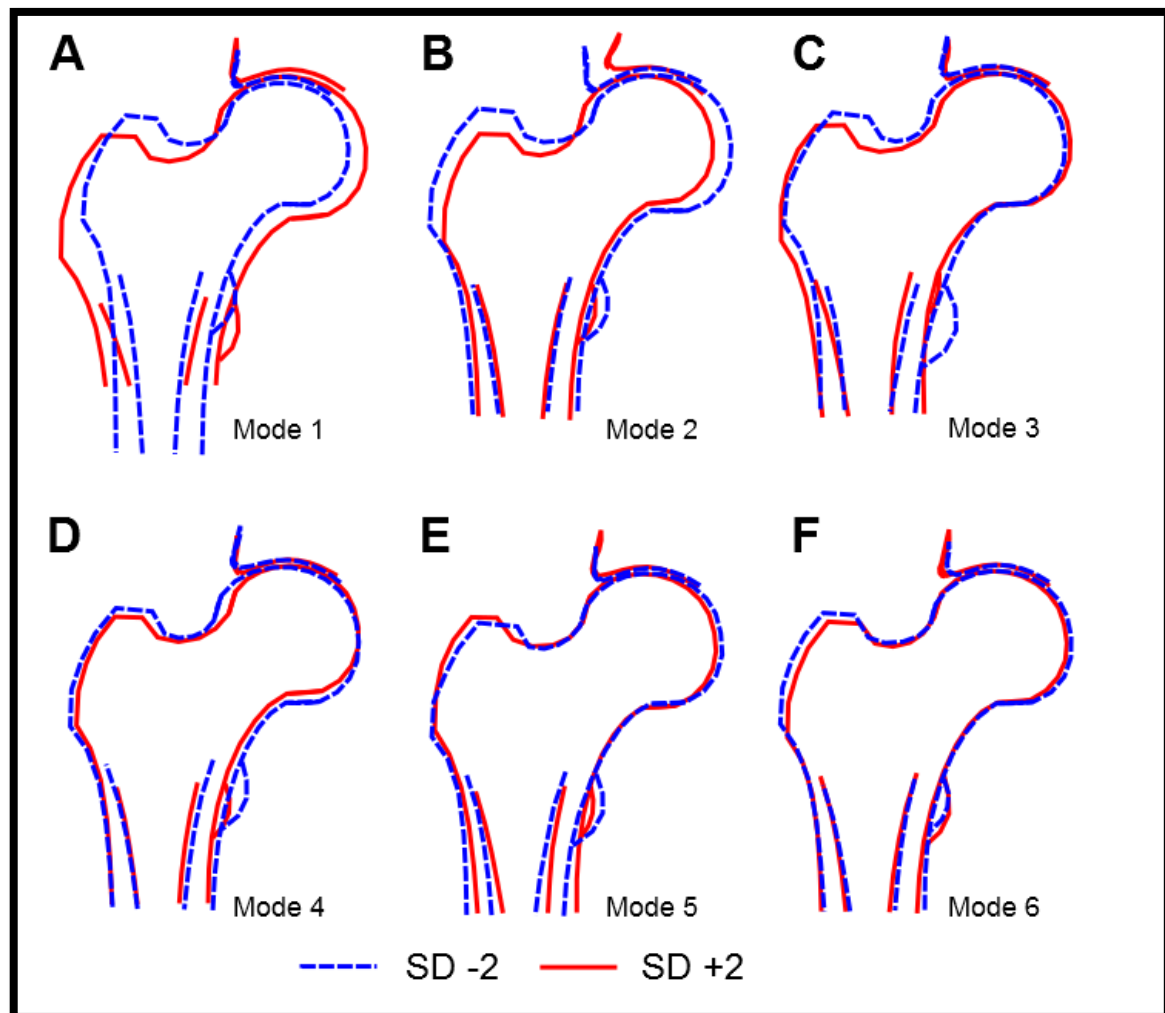


Figure 9-3: The six hip shape modes from TASOAC cohort.

A) Mode1: changes in femoral head and neck (lower aspect), greater trochanter along with longer shaft. B) Mode 2: changes in the femoral head and neck (upper aspect), acetabulum and greater trochanter. C) Mode 3: specific shape variations in the upper femoral neck, greater trochanter, and shaft. D) Mode 4: femoral head (upper aspect) and longer femoral shaft. E) Mode 5: larger greater trochanter and shaft in comparison to the femoral head. F) Mode 6: mild changes in greater trochanter and acetabulum.

Statistical analyses

Characteristics of the population were summarized as means and standard deviations or as percentages and frequencies. At baseline, the associations of hip shape mode scores with the presence of hip pain and radiographic features were assessed using log binominal regression analyses. Pairwise Pearson's correlations were used to calculate the correlations of hip shape mode scores with age, body mass index (BMI), hip cartilage volume and leg strength while a generalized linear model was applied to calculate the link between hip shape mode scores and sex. At follow up, to estimate the longitudinal associations of baseline hip shape with the presence of hip pain, MRI-based structural findings and THR, log binomial regression was used. Linear regression analyses were used to investigate the longitudinal associations of baseline hip shape mode scores with hip pain severity. To examine the correlations between hip shape, hip BMLs and effusion-synovitis size, again pairwise correlation coefficients were applied. All models were adjusted for age, sex and body mass index (BMI). Follow up data (phase 2 and 3, plus phase 4 for THR) were combined in analyses, and the correlation between repeated measurements on individuals was taken into account by adjusting standard errors using the sandwich (robust) estimator of variance.¹⁸⁷⁻¹⁸⁹ All statistical analyses were performed using Intercooled STATA 12 (Stata Corp, College station, Texas, USA).

Results

Characteristics of the study population

A summary of characteristics of the sample population is presented in Table 9-1 and a graphical summary of the significant changes in mode scores resulting in an increased prevalence may be found in figure 9-4. At baseline, the average age of the subjects was 63 years; they were overweight, 49% of the subjects were males and 41% had hip ROA. At follow up, the proportion with hip pain was slightly greater than the proportion with self-reported hip pain at baseline (47% vs. 42%). During the time frame of ten years, 29 subjects underwent THR. Overall, only about one-fifth of the

cohort had a hip BML whereas about three-quarters had a high cartilage signal and hip effusion-synovitis.

Table 9-1: Characteristics of the TASOAC cohort

Characteristics	Mean (S.D) (n=831)
Baseline	
Age (yrs.)	63.2 (7.45)
Sex (Males)	49%
Body Mass Index (BMI)	27.7 (4.63)
Hip cartilage volume (cm ³)	5340 (1100)
Presence of hip pain (Y/N)	42%
Radiological hip OA (ROA) (Y/N)	41%
Follow up *	
Presence of hip pain (WOMAC) (Y/N)	47%
Hip pain score (WOMAC)	2.60 (5.24)
Leg strength (kg)	93.1 (48.5)
Presence of hip bone marrow lesions (BMLs) (Y/N)	18%
Hip BML size (CSA) (cm ²)	0.20 (0.52)
Presence of hip cartilage defects (Y/N)	72%
Presence of high cartilage signal (Y/N)	74%
Presence of hip effusion-synovitis (Y/N)	95%
Hip effusion-synovitis size (CSA) (cm ²)	1.96 (1.60)
Total hip replacement (Y/N) **	2.64%

Data presented as means and standard deviations or percentages and frequencies

BMD= bone mineral density

WOMAC= Western Ontario and McMaster Universities Osteoarthritis

CSA= cross-sectional area

* Includes data from phase2 and phase3

** Includes all hip replacements (left or right) from all follow-up assessments

The patterns of variation for each of modes 1 to 6 are shown in Figure 9-3. Modes are determined in order of the fraction of the total variance they contain. These six modes explained 68% of the total variation in the population. Modes 1 and 2 together described 45% of the variance and all were greater than 3.5%. Mode 2 was not associated with sex. Prevalence ratios for females and males were for mode 1, PR = 0.84 ($P < 0.001$), indicating men had, on average, higher mode 1 scores than females, while higher scores for modes 3-6 were more common among females (range of PR: 1.16-1.35, $P < 0.001$).

Associations of hip shape with pain and radiographic features at baseline

Table 9-2 presents associations of hip shape with hip pain and radiographic features of hip OA at baseline. Self-reported hip pain was not associated with shape but modes 2 and 6 were associated with the presence of ROA. Analysis of the components of ROA showed that several modes were associated with different features of hip ROA. For instance, lower scores of modes 1 and 2 showed a weak relationship with the presence of JSN and lower mode 4 scores were associated with increased prevalence of osteophytes. Mode 6 was positively associated with all the major features of ROA with each standard deviation increase in score corresponding to a 23%, 15% and 13% higher prevalence of JSN, osteophytes and hip ROA, respectively.

Table 9-2: The associations of hip shape with hip pain and radiographic features of hip OA at baseline.

Hip shape modes	Presence of hip pain <i>PR (95%CI) *</i>	Presence of hip joint space narrowing (JSN) <i>PR (95%CI) *</i>	Presence of hip osteophytes (OST) <i>PR (95%CI) *</i>	Presence of hip radiographic OA <i>PR (95%CI) *</i>
1	1.03 (0.92, 1.14)	0.88 (0.78, 0.99)	0.94 (0.82, 1.09)	0.94 (0.84, 1.05)
2	0.99 (0.90, 1.11)	0.76 (0.70,0.85)	1.05 (0.91, 1.22)	0.85 (0.76, 0.95)
3	0.97 (0.90, 1.08)	0.96 (0.85, 1.09)	1.09 (0.94, 1.26)	0.98 (0.90, 1.11)
4	0.97 (0.90, 1.08)	1.03 (0.91, 1.17)	0.79 (0.70,0.92)	1.07 (0.95, 1.20)
5	1.04 (0.93, 1.17)	0.93 (0.83, 1.06)	0.94 (0.81, 1.09)	0.93 (0.82, 1.04)
6	0.96 (0.90, 1.07)	1.23 (1.09, 1.40)	1.15 (1.00, 1.33)	1.13 (1.01, 1.27)

Independent variable: hip shape modes at baseline. Dependent variable: Presence of hip pain, ROA, JSN and OST at baseline.

*PR (95%CI) = prevalence ratios (95% confidence intervals) adjusted for age, sex and body mass index at baseline.

Bold text represent statistically important results.

Correlations of shape modes at baseline

Correlations of hip shape modes with age, BMI, and baseline MRI-based structural findings are presented in Table 9-3. Although small some of these correlations were significant. Age at baseline was significantly associated with lower mode 2 scores, describing a wider neck, loss of joint space and greater femoral head coverage. Lower scores for modes 1-4 were modestly correlated with greater BMI. Greater mode 1 scores, along with lower scores for modes 3-6, were associated with greater leg strength and greater hip cartilage volume.

Table 9-3: Correlations of hip shape modes with age, BMI and MRI-based structural

Hip shape modes	Baseline age (yrs.)	Baseline BMI (kgs/m ²)	Baseline leg strength (Kg)	Baseline hip cartilage volume (cm ³)
	<i>Correlation</i> (<i>r</i>)	<i>Correlation</i> (<i>r</i>)	<i>Correlation</i> (<i>r</i>) [†]	<i>Correlations (r)</i> [†]
1	-0.04	-0.12 ***	0.20 ***	0.40 ***
2	-0.13 ***	-0.07 *	0.00	-0.03
3	-0.03	-0.11 ***	-0.15 ***	-0.20 *
4	-0.04	-0.10 ***	-0.13 ***	-0.25 ***
5	-0.04	-0.04	-0.22 ***	-0.13
6	-0.04	-0.02	-0.13 ***	-0.21 *

Independent variable: hip shape modes at baseline. Dependent variable: hip cartilage volume (baseline), hip BML CSA and hip effusion-synovitis CSA.

* denotes P<0.05, ** denotes P<0.01 and *** denotes P<0.001

†Correlations adjusted for age, sex and body mass index at baseline.

Bold indicates statistically significant results.
findings at baseline

Shape modes and pain at follow-up

Although not associated with the presence of hip pain at baseline, hip shape was associated with the presence and severity of hip pain at follow-up (Table 9-4). Higher mode 1 scores and lower scores for modes 3 and 6 predicted an increase in the prevalence of hip pain at follow-up. Mode 3 score was also negatively associated with the severity of pain.

Table 9-4: Associations of hip shape modes at baseline with presence and severity of

Hip shape	Presence of hip pain	Severity of hip pain
Modes	PR (95%CI) *	β coefficient (95%CI) **
1	1.09 (1.00,1.20)	0.17 (−0.20, 0.55)
2	0.99 (0.91, 1.09)	−0.13 (−0.50, 0.21)
3	0.91 (0.82, 0.99)	−0.43 (−0.84, −0.02)
4	0.99 (0.90, 1.09)	−0.12 (−0.55, 0.30)
5	1.03 (0.94, 1.14)	0.10 (−0.24, 0.45)
6	0.91 (0.84, 0.99)	−0.05 (−0.40, 0.30)

Independent variable: hip shape modes at baseline. Dependent variable: Presence of hip pain (yes/no) and hip pain score (hip WOMAC score ranging from 0-45) at follow up.

*PR (95%CI)= prevalence ratios (95% confidence intervals) adjusted for age, sex, body mass index with clustering of observation on subjects at phase2 and phase3 taken into account.

** β co-efficient (95% confidence intervals) adjusted for age, sex and body mass index and with clustering of observation on subjects at phase 2 and phase 3 taken into account.

Bold text represents statistically significant results.

hip pain at follow-up

Shape modes at baseline, especially modes 2 and 4, also correlated with MRI-based hip structural changes at follow-up (Table 9-5). Mode 4 was strongly associated with the presence of both BMLs and high cartilage signal, and lower scores indicated a greater prevalence of both. It was also negatively correlated with BML size and effusion-synovitis size, although not the presence of multiple effusion-synovitis. Lower scores were also strongly associated with a greater prevalence of THR over the study period. A change of -1 SD in mode 4 predicted 40% greater prevalence of hip BMLs. Both the presence and the size of an effusion-synovitis were positively associated with increasing values for mode 2. Interestingly, modes 2 and 4 were both strong predictors of THR.

Table 9-5: Associations of hip shape modes at baseline with MRI based structural findings and total hip replacement (THR) at follow up.

Hip shape mode	Presence of any hip BMLs	Presence of high cartilage signal	Presence of hip effusion-synovitis at two or more sites	THR	BML CSA (cm ²)	hip effusion-synovitis CSA (cm ²)
	PR (95%CI) *	PR (95%CI) *	PR (95%CI) *	PR (95%CI) *	<i>Correlations (r)[‡]</i>	<i>Correlations (r)[‡]</i>
1	1.30 (0.92, 1.81)	1.03 (0.92, 1.20)	1.12 (0.91, 1.40)	0.84 (0.63,1.12)	0.06	0.20***
2	1.22 (0.89, 1.70)	1.06 (0.96, 1.20)	1.22 (1.00, 1.50)	1.60 (1.20,2.15)	0.08	0.21***
3	1.12 (0.82, 1.52)	1.04 (0.93, 1.15)	0.95 (0.77, 1.20)	0.75 (0.60, 1.00)	-0.00	-0.10
4	0.60 (0.42, 0.82)	0.89 (0.80, 0.99)	1.13 (0.92, 1.41)	0.63 (0.50, 0.84)	-0.13*	-0.11*
5	0.82 (0.60, 1.14)	1.02 (0.91, 1.15)	0.88 (0.72, 1.08)	1.34 (0.99, 1.80)	-0.09	0.07
6	0.90 (0.62, 1.30)	0.97 (0.87, 1.08)	0.91 (0.71, 1.20)	0.96 (0.72, 1.30)	-0.07	0.00

Independent variable: hip shape modes at baseline. Dependent variable: clinical, structural factors at follow up.

*PR (95% CI)= prevalence ratios (95% confidence intervals) adjusted for age, sex and body mass index with clustering of observation on subjects at phase2 and phase3 taken into account.

‡Correlations adjusted for age, sex and body mass index with clustering of observation on subjects at phase2 and phase3 taken into account.

Baseline									
Mode	Pain- baseline	JSN - baseline	OsPhy- baseline	rhOA- baseline	Age- baseline	BMI- baseline	Legstrngt h-	Cart-Vol- baseline	Sex (M vs. F)
1	-	↓	-	-	-	↓	↑	↑	↑
2	-	↓	-	↓	↓	↓	-	-	-
3	-	-	-	-	-	↓	↓	↓	↓
4	-	-	↓	-	-	↓	↓	↓	↓
5	-	-	-	-	-	-	↓	-	↓
6	-	↑	↑	↑	-	-	↓	↓	↓
FU									
Mode	BML	Effusion-	Pain Presence	Pain Severity	BML-	HighCart Signal-	HipEffusi on(>1site THR)		
1	-	↑	↑	-	-	-	-	-	
2	-	↑	-	-	-	-	↑	↑	
3	-	-	↓	↓	-	-	-	-	
4	↓	↓	-	-	↓	↓	-	↓	
5	-	-	-	-	-	-	-	-	
6	-	-	↓	-	-	-	-	-	

Figure 9-4: Summary of the results at baseline and follow up

Discussion

This is the first study to link the predictive power of SSM for ROA & THR to BMLs and effusion-synovitis in addition to pain and anthropometric data. In this population-based cohort, SSM was used to quantify the shape of the proximal femur and acetabulum. By comparing the shape at baseline with participant data at baseline and over the following 10 years, we have identified features of hip shape that are associated with both the incidence and the progression of hip OA. These associated features and outcomes include pain, BMLs, effusion-synovitis and total hip replacement. In addition, morphological variation was found between males and females with higher scores for mode 1 and lower scores for modes 3-6 being more common in males. Mode 1 represents the largest changes and is associated with increasing head size and femoral neck length and width (Figure 9-3).

Baseline: Leg strength and radiographic features

Interestingly, these modes had similar positive associations with greater hip cartilage volume and leg strength, even after correction for sex. Associations with ROA were largely negative and no association was found with pain. Lower mode 1 scores, for instance, indicating a shorter, narrower femoral neck, were associated with greater joint space narrowing. Surprisingly, none of the first 6 modes showed any variation in the location of the points marking the positions of osteophytes although modes 4 and 6 both predicted the presence of osteophytes as seen in the images.

Decreasing scores for mode 2 identified characteristics such as increasing acetabular coverage, a smoother transition of the upper femoral head into the femoral neck, increasingly non-spherical femoral head and larger greater trochanter, some of which may indicate a pistol-grip-like deformity.¹⁷² At baseline, a lower score for this mode associated with greater prevalence of both JSN and ROA. Lower scores of mode 4, with prominent features of pistol group deformity, along with higher mode 6 scores, which represented those with a flatter femoral head, short femoral neck and sharp transition of the femoral head into the neck were associated with a greater prevalence of osteophytes. Associations of shape modes with hip ROA have been previously published and variations in the shape of the femoral head, its transition into the

superior aspect of the neck and the length of the femoral neck have been reported to be associated with risk of hip ROA.[170](#), [182-184](#), [259](#), [260](#)

Follow-up

Hip pain and shape modes

Higher scores of mode 1 and lower scores of mode 6 were associated with incident hip pain. Lower mode 3 scores were associated with greater prevalence and severity of hip pain. Lower scores of mode 3 included shorter femoral neck and sharp transition of lower femoral head into femoral neck. Previous studies have shown that morphological variations in the femoral neck are predictive of hip pain.[183](#), [262](#) Modes 1 and 6 were associated not only with radiographic features (at baseline) but mode 1 also correlated with hip effusion-synovitis CSA (at follow-up). These factors might explain the associations of these modes with hip pain. Overall, our results are consistent with previous studies that have demonstrated associations between shape modes and hip pain.[183](#), [260](#)

Structural changes and hip shape

Modes 2 and 4 appear to associate strongly with structural changes in the subchondral bone of the hip which are risk factors for progression of OA.[215](#), [229](#) For instance, at baseline, lower scores of these modes associated with greater JSN and prevalence of osteophytes respectively. Similarly, at follow-up, a low score for mode 4 predicted OA-related features such as higher probability of the presence of BMLs, high cartilage signal and correlated with larger BML and hip effusion-synovitis size. In contrast, greater values for mode 2 were found to be associated with effusion-synovitis and THR. Features highlighted by both these modes corresponds to cam deformity and pistol grip deformity (Figure 9-3), which are well known risk factors for development of hip OA.[172](#), [263](#) As this is the first study to identify the link between hip shape and structural changes such as BMLs, there are no previous data exploring the association; these morphological features could encourage structural changes in the subchondral bone and cartilage.[170](#), [182](#), [259](#), [260](#)

Higher scores of both modes 1 and 2 modestly correlated with larger effusion-synovitis CSA and a +1 SD higher mode 2 score predicted a 22% greater prevalence of the presence of hip effusion-synovitis. In further analyses, longitudinal associations were found between baseline shape and change in hip effusion-synovitis (from phase 2 to phase 3). Over this period, a one SD lower baseline mode 1 score was associated with greater hip effusion-synovitis CSA (*Beta*: -0.20; 95%CI: -0.30, -0.06), whereas no association was found with mode 2. Mode 1 thus appears to be predictive not only of pain but also effusion-synovitis and future studies will explore whether this is an early indicator of later ROA as suggested by other studies.¹⁴⁷

Total hip replacement and shape modes

The same two modes that associated most strongly with MRI structural features, modes 2 and 4, also showed the strongest associations with hip replacement. Increasing mode 2 associated with increasing effusion-synovitis and decreasing mode 4 scores also predicted increasing effusion-synovitis along with BMLs and high cartilage signal. Every +1 SD change in mode 2 increased the risk of THR by about 60% and a -1 SD change in mode 4 increased the risk of THR by about 40%. Both these modes identified shape patterns related to OA such as the transition of the femoral head into the femoral neck, the size of the greater trochanter a flattening of the femoral head itself and mode 2 captured coverage of the femoral head by the acetabulum¹⁸³. Overall, improper coverage of femoral head by the acetabulum also known as femoral-acetabular impingement (FAI), along with features related to pistol grip deformity are known to associate with greater risk of hip OA.^{172, 173, 263}

Limitations

A number of limitations need to be noted. This study uses DXA images of the left hip while MRI-detected anomalies were measured in the right hip, so the joint appearances may not be directly comparable. Nevertheless, it has been demonstrated that OA in the ipsilateral joint strongly predicts and associates with OA in the contralateral joint and studies using SSM have reported similar results.^{264, 265} Recently statistical shape modelling has been upgraded to adjust automatically for shape variations attributable for subject positioning. One such study demonstrated that

proximal left and right femur were highly symmetrical.¹⁸⁵ The effect of the internal / external rotation of the femur, arising from variations in patient positioning, cannot be ruled out and even when using standardized protocols in which the position of the feet is carefully controlled, this might influence the DXA images. Nevertheless, SSM has the potential to pick up the effects of rotation from the variation in shape during the development of the model.^{170, 175, 183}

Conclusion

In this population-based study, two-dimensional hip shape measured on entry to the study is shown to be associated with not only with ROA and muscle strength at baseline but is also predictive of THR, hip pain, BMLs, effusion-synovitis and hip structural changes occurring up to 10 years later. These data suggest that different morphological features identified by shape modes have relevance for multiple facets of hip osteoarthritis, both radiographic and clinical. It adds further evidence for the possible use of SSM as an imaging biomarker for the incidence and progression of OA.

Postscript

In this chapter we demonstrated how statistical shape modelling (SSM) could be used to assess bone shape in a large cohort. Subsequently, hip bone shape associated with several factors which are relevant for hip OA. The following chapter discusses all the main findings presented in this thesis along with implications and future directions.

Chapter 10 : Discussion and future directions



Background

Musculoskeletal disorders such as OA are the dominant source of chronic pain.¹⁰ OA has a considerable physical and psychological impact on individuals and on health care systems.^{10, 12} It's one of the most common forms of arthritis and the hip is the second most frequently affected joint. Hip OA is a slow and progressively debilitating disease leading to pain, joint stiffness and lower quality of life which eventually leads to the destruction of the joint.^{266, 267}

Despite the large disease burden, there are no proven or totally effective strategies to manage and control OA. Orthodox treatments of OA remain palliative and expensive, and do not target disease progression. New techniques such as cartilage regeneration remain experimental, and there is no certainty that replacing the cartilage would halt the development of the disease.

Radiographic measures for assessment of hip OA are adequate but x-rays are two-dimensional and structures other than bone are invisible. In comparison to X-ray, MRI is functionally superior and is the imaging modality of choice. Treatment strategies for hip OA will not improve the mechanisms behind its cause, progression and consequences have been better investigated. The novel findings from this research make some important preliminary contribution to the understanding of the determinants of hip OA.

The following sections describe the primary findings of the studies presented in this thesis followed by implications and directions for future research.

Main Findings

Chapter 4 outlines associations between hip BMLs, hip and knee pain and high cartilage signal. In this community-based population, 28% had either femoral or/and acetabular BML. Of these, 8% of the subjects had a large hip BML. Cross-sectionally, those with larger hip BMLs had greater hip pain. In longitudinal analyses, an incident of larger BMLs was independently associated with an increase in hip pain. Furthermore, resolving femoral BMLs was associated with a decrease in knee pain.

Chapter 5 extends the findings from chapter 4, and describes the cross-sectional and longitudinal associations between hip BMLs and BMD. In this study, irrespective of BML size, hip BMLs were associated with hip and femoral neck BMD but not with spine BMD. Unexpectedly, these associations varied according to site of the BML. For instance, femoral BMLs associated with higher femoral neck BMD, and acetabular BMLs associated with lower total hip and femoral neck BMD.

Chapter 6 examines the cross-sectional associations of hip cartilage defects with clinical, demographical, structural and radiographic features relevant to hip OA. The overall prevalence of hip cartilage defects, irrespective of the extent of cartilage damage was 76%. In this cohort, correlates of hip cartilage defects were somewhat influence by sex. Greater hip cartilage damage was noted in subjects who had higher hip pain, greater proportion of hip BMLs, larger hip effusion-synovitis and early radiographic changes. Physical activity and leg strength were also associated with hip cartilage defects.

Chapter 7 describes the associations of hip effusion-synovitis. Cross-sectionally, the extent of hip effusion-synovitis associated with higher prevalence of hip pain and femoral defects associated with larger hip effusion-synovitis size. Longitudinally, independent of each other, persistent hip BMLs and incident hip cartilage defects predicted 32-60% increase in hip effusion-synovitis CSA. Moreover, independent of presence of hip effusion-synovitis, hip cartilage defects predicted incident and worsening of hip BMLs and vice versa.

Chapter 8 describes the associations between hip muscle CSA and BMD at the hip, femoral neck, and spine. Muscle CSA of the hip rotators and flexors were modestly associated with muscle strength and BMD. Hip flexors had a stronger relationship with BMD for women than for men. Unexpectedly, a link between gamelli muscle CSA and spine BMD was found and gluteus maximus showed no associations.

In chapter 9, shape of the proximal femoral head was quantified using statistical shape modelling. The first six shape modes were extracted and their associations at baseline and over the period of 10 years were described. Most of shape modes were associated with hip cartilage volume and muscle strength but some were specifically associated with particular features of hip OA. At baseline, modes 1, 2, 4 and 6 were associated with radiological features. Over time, hip shape features represented by modes 1, 2

and 3 influenced clinical factors relevant for OA such as hip pain and hip effusion-synovitis. However, increasing score of mode 2 also predicted a higher risk of THR. Mode 4, was strongly associated with structural changes at the hip joint and also predicted greater risk of THR. While mode 2 showed characteristic of FAI, mode 4 presented with features of pistol grip deformity. Overall, the shape of the hip joint is an important feature and this hypothesis-generating study demonstrates that morphological features identified by shape modes are relevant for hip osteoarthritis.

Strengths and limitations

Strengths

Most of the studies presented in this thesis are novel because large population based studies at the hip are rare.

The TASOAC cohort is a community-based study in which all subjects were randomly selected with equal number of men and women. This cohort is unique, as most of previous data on hip is based on cohorts with mild or severe hip OA and the severity of the disease makes it difficult to understand pathophysiology OA in such samples. Thus, the cohort used in this thesis is generalizable and included mostly healthy older adults. Such a study sample provides opportunities to examine the pathophysiology of the disease in preclinical stages.

TASOAC is an ongoing prospective study which includes four-time points with an extensive set of MRI/DXA images and clinical data which was collected using standardized protocols. The data collected included potential mediators, effect modifiers, and confounders that could be used to in the analytical process. This provides unparalleled opportunities for combining quantitative analyses to study the determinants of hip OA.

The study presented in chapter 9 is the first large Australian-based study to use ASM/SHAPE imaging software for assessing the global morphology of the hip.

The findings presented in this thesis helps to fill in a few of the gaps and improve our understanding of the determinants of early hip OA.

Limitations

Limitations relevant to each study have been described in chapters 4-9 of this thesis.

As this is a large cohort and due to budget limitations, hip MRIs for all the participants included the TASSOAC study were not done. Many of the associations are cross-sectional so one cannot determine causal pathways. In addition, many associations are inconsistent and/or data driven meaning replication in other cohorts is desirable.

This thesis aimed to understand a few mechanisms behind development of hip OA and several relevant features for hip OA were measured, but there may be a few other unmeasured factors such as labrum (rim of soft tissue or fibrocartilage which provides joint stability and protects cartilage) which could also play a role in progression of hip OA.

Implications

The aim of this thesis was to study the hip as a whole and describe the associations of major factors involved in the pathogenesis of hip OA and if possible explain the conceivable mechanisms.

Pain and BMLs

Pain in OA is multifactorial, and in this thesis we established the link between large hip BMLs and hip pain. Hence, BMLs are one of the potential causes for hip pain and may lead to referred knee pain in older adults with early hip OA. Hip BMLs associate with early changes in the hip cartilage.

Bone density and BMLs

For the first time, a cross-sectional and longitudinal association between hip BMLs and local bone density was reported and established in a population-based cohort. Hypothetically, BMLs might represent disease pathology which includes demineralization of the bone.

Hip cartilage defects

Correlates of hip cartilage defects were extensive. In early stages of hip OA, hip cartilage defects not only associate with hip pain but also with several structural and radiological findings. Thus, structural changes in the joint are linked with the cartilage and may have a deleterious effect on the cartilage and vice versa. Changes in the hip cartilage might influence leg strength or vice versa and physical activity may be beneficial for hip cartilage.

Hip effusion-synovitis

For the first time, the associations of hip effusion-synovitis were described in a community-based cohort. Hip effusion-synovitis associates with hip pain, hip cartilage defects, and hip BMLs, but not with early hip radiographic changes. Hip BMLs and hip cartilage defects are co-dependent on each other and predict larger effusion-synovitis. Our studies suggest that in early hip OA there are shared underlying pathways between effusion-synovitis, hip cartilage defects, hip BMLs and changes in the bone which may eventually manifest as pain, inflammation, and joint deterioration.

Muscles CSA, muscle strength, and bone density

In older adults, hip muscle CSA (mostly flexors) associated with BMD and muscle mass modestly associates with leg strength. Biological differences in muscle mass by sexes and case-to-case are obvious, and this study suggests that targeted strengthening of certain muscles may be useful in attaining preservation of muscle mass and perhaps increase joint stability.

Bone shape and early OA

X-rays may be adequate but are insensitive towards early signs of OA. Global assessment of the hip shape using SSM might be a more accurate and better way of predicting and tracking the progression of hip OA.¹⁷⁰ The ASM/SHAPE imaging software's can extend the application of X-ray and DEXA images in clinical practice as these are usually performed for older adults. SSM can be used to predict and identify those at higher and lower risk of developing hip OA. In general, use of SSM might simplify monitoring, tracking and examining bone changes in those with OA at the hip and/or other joints affected by OA.

Future directions

Observational studies

This thesis provides an extensive (mostly preliminary) research on early hip OA. A population-based study including subjects with moderate to severe hip OA would be very beneficial. A comparison between almost healthy cohort such as TASSOAC and a sample population with advanced disease is necessary for understanding the unpredictable nature of hip OA.

BMLs play a key role in OA because they are not only linked with clinical symptoms but also associate with changes in the bone density. This is an interesting concept which requires further study. Advanced techniques such as pQCT (peripheral quantitative computed tomography) or Micro-CT (Micro-computed tomography) provide a better information about the bone structure and cover several parameters determining bone health.¹⁵¹ A study, using these techniques and comparing the differences in bone health in those with or without BMLs could provide further insight in to the pathophysiological mechanisms between BMLs and BMD.

Another method which could aid in understanding the relationship between subchondral BMLs and BMD is by using Active Appearance Models (AAM)^{268, 269} Unlike ASM, AAM models are designed to identify differences in the quality or texture of bone. Such statistical shape models have been successfully applied to predict hip fractures. This method may not provide as many measurements as pQCT and Micro-CT, and is dependent on the quality of x-ray or DEXA images, but it is

economical and can be applied in cohorts where the data is already collected. In general, finding from such studies could highlight the fact that BMLs present in OA could be a potential target for future interventions.

Cartilage is at the heart of the disease process in OA, but studying hip cartilage is challenging. Applying methods such as T2 mapping and SSM could aid in quantification of hip cartilage. There is current evidence that both T2 mapping and SSM can be applied to produce 3D models of the knee cartilage²⁷⁰. Such data cannot be derived from traditional semi-quantitative methods. A pilot longitudinal study investigating cartilage using 3D models could provide the whole picture of the extent of cartilage damage in both symptomatic and asymptomatic subjects.

Hip effusion-synovitis still remains under-investigated. Several researchers have reported the roles of knee effusion-synovitis.^{134, 143} Although, our study in chapter 7 highlights the correlates of hip effusion-synovitis, further research exploring the role of hip effusion-synovitis are needed. Future studies using advanced imaging modalities such as gadolinium to assess hip effusion-synovitis could be useful in understanding the extent of the role of joint fluid in hip OA.

SSM models can be modified to identify other risk factors of hip OA such as FAI (femoroacetabular impingement) in young and older adults.

Clinical trials

In the preliminary research conducted in this thesis, several structural abnormalities such as BMLs, cartilage defects, effusion-synovitis and high cartilage signal were identified. A clinical trial investigating if interventions targeting one structural abnormality also reduces/effects of other structural abnormalities. Also, to identify if separate or combination of interventions would be required to slow down the structural damage.

Clinical trial aiming to examine longitudinal relationship between hip cartilage, hip muscles, and physical activity. Such longitudinal study could identify the benefit or risk of various types of physical activity, and can include young and older adults.

Conclusions

Overall, structural changes are slow and relatively uncommon in the preclinical stages of hip OA. Nevertheless, hip BMLs, hip cartilage defects, high cartilage signal and hip effusion-synovitis are inter-related and contribute to changes in the subchondral bone; with a probable role in the pathogenesis of hip OA. Additionally, muscle bulk and strength could aid in the preservation of bone density and assessing bone shape using ASM could benefit in improving assessment and monitoring of disease progression and identifying those at higher risk of OA.

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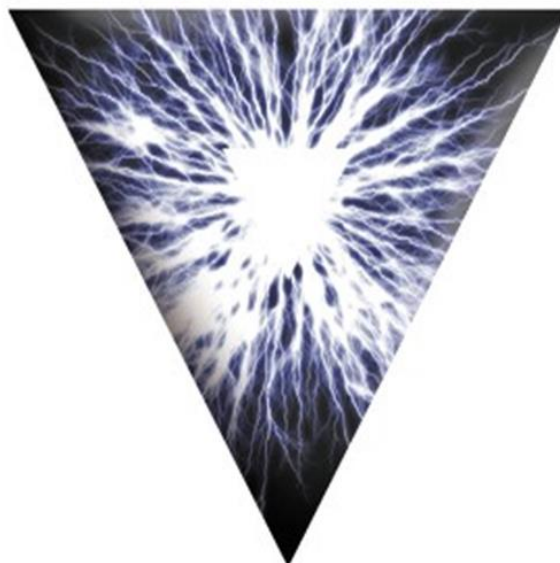
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Chapter 12 Appendices



Appendix I: An example of Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index for assessing hip pain.

Rate the following today for HIPS

3.3. This section assesses pain, stiffness and functional deficit on a scale from 1 - 10

Example

Example of no pain

none

☒ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

severe

Example of severe pain

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☒ 10

1. Referring to your hips only how much pain do you experience when

none

severe

a. Walking on a flat surface

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

b. Going up and down stairs

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

c. At night while in bed

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

d. Sitting or lying

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

e. Standing upright

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

2. Referring to your hips only how much stiffness do you experience

none

severe

a. After first awakening

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

b. Later in the day

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

3. Referring to your hips only how much functional deficit do you experience when

none

severe

a. Descending stairs

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

b. Ascending stairs

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

c. Rising from bed

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

d. Rising from sitting

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

e. Putting on socks

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

f. Taking off socks

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

g. Bending to the floor

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

h. Lying in bed

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

Question 3 continued	none									severe
i. Walking on flat surface	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10
j. Getting in/out of the bath	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10
k. Standing	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10
l. Sitting	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10
m. Getting in/out of the car	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10
n. Getting on/off the toilet	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10
o. Heavy domestic chores	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10
p. Light domestic chores	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10
q. Shopping	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	<input type="radio"/> 6	<input type="radio"/> 7	<input type="radio"/> 8	<input type="radio"/> 9	<input type="radio"/> 10

Appendix II: An example of Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index for assessing knee pain.

Rate the following today for KNEES

3.2. This section assesses pain, stiffness and functional deficit on a scale from 1 - 10

Example

Example of no pain

none

☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

severe

Example of severe pain

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☒ 10

1. Referring to your knees only how much pain do you experience when

- | | none | | | | | | | | | | severe |
|------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------|--------|
| a. Walking on a flat surface | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| b. Going up and down stairs | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| c. At night while in bed | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| d. Sitting or lying | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| e. Standing upright | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |

2. Referring to your knees only how much stiffness do you experience

- | | none | | | | | | | | | | severe |
|--------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------|--------|
| a. After first awakening | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| b. Later in the day | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |

3. Referring to your knees only how much functional deficit do you experience when

- | | none | | | | | | | | | | severe |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------|--------|
| a. Descending stairs | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| b. Ascending stairs | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| c. Rising from bed | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| d. Rising from sitting | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| e. Putting on socks | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| f. Taking off socks | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| g. Bending to the floor | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |
| h. Lying in bed | <input type="radio"/> 1 | <input type="radio"/> 2 | <input type="radio"/> 3 | <input type="radio"/> 4 | <input type="radio"/> 5 | <input type="radio"/> 6 | <input type="radio"/> 7 | <input type="radio"/> 8 | <input type="radio"/> 9 | <input type="radio"/> 10 | |

Question 3 continued

none

severe

i. Walking on flat surface

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

j. Getting in/out of the bath

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

k. Standing

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

l. Sitting

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

m. Getting in/out of the car

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

n. Getting on/off the toilet

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

o. Heavy domestic chores

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

p. Light domestic chores

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

q. Shopping

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10


Appendix III: An example of pedometer dairy used in TASSOAC Phase 2

TASSOAC PEDOMETER DIARY Phase 2 Round 1

Name.....TASSOAC ID Pedometer number
 Sensitivity number..... **Remember to reset Pedometer Daily.**

Day	Date	Start time	End time	Display number	Time spent NOT wearing pedometer Whilst participating in physical activity	Name activity participated in whilst not wearing pedometer	List any circumstances which may have affected pedometer reading
1							
2							
3							
4							
5							
6							
7							

Appendix IV: An example of pedometer dairy used in TASOAC Phase 3

9152355965		 Menzie's Research Institute		TASOAC -- PHASE 3 --PEDOMETER DIARY		Study ID No. 	
REMEMBER TO RESET YOUR PEDOMETER EVERY MORNING							
Day	Date	Start Time <small>Please use 24hr Times</small>	End Time	Display Number <small>from the Pedometer at the end of the day</small>	Time spent active but no pedometer <small>Hrs : Mins</small>	Activities participated in while NOT wearing pedometer	Circumstances that may have affected pedometer reading
eg.	1 5 / 0 1 / 0 7 <small>i.e. 15th Jan 2007</small>	0 7 : 1 5 <small>i.e. 7:15am</small>	2 2 : 3 0 <small>i.e. 10:30 pm</small>	 9 5 7 8 <small>i.e. 9578 steps counted by the pedometer for the day</small>	 1 : 1 5 <small>i.e. 1hr and 15mins active without pedometer</small>	Swimming	Operating heavy machinery
1	 / / 	 : 	 : 	 	 : 		
2	 / / 	 : 	 : 	 	 : 		
3	 / / 	 : 	 : 	 	 : 		
4	 / / 	 : 	 : 	 	 : 		
5	 / / 	 : 	 : 	 	 : 		
6	 / / 	 : 	 : 	 	 : 		
7	 / / 	 : 	 : 	 	 : 		

Office use only:

Ped ID 	Issue Date / / 	Return Date / /
--	--	---

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Ahedi, H., Aitken, D., Blizzard, L., Cicuttini, F., Jones, G., (2013). A population-based study of the association between hip bone marrow lesions, high cartilage signal, and hip and knee pain, *Clinical rheumatology*, 33(3), 369-376.

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Ahedi, H., Aitken, D., Blizzard, L., Cicuttini, F., Jones, G., (2013). The association between hip bone marrow lesions and bone mineral density: a cross-sectional and longitudinal population-based study, *Osteoarthritis and cartilage*, 21(10), 1545-1549

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Ahedi, H., Aitken, D., Scott, D., Blizzard, L., Cicuttini, F., Jones, G., (2014). The association between hip muscle cross-sectional area, muscle strength and bone mineral density, *Calcified tissue international*, 95(1), 64-72. The final publication is available at Springer via <http://dx.doi.org/10.1007/s00223-014-9863-6>